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COMMUNICATIONS

EPIDEMIC KERATO-CONJUNCTIVITIS IN THE MIDDLE EAST*

Clinical and Experimental Study

BY

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THE following is our experience of so-called keratitis superficialis punctata epidemica during several years in the Middle East, particularly in Palestine. The report consists of a clinical and an experimental part.

(A) Clinical part

In 1937 and 1938 sporadic cases of so-called keratitis superficialis punctata began to appear and later the disease assumed epidemic proportions. Colleagues working in the coastal area of Palestine were the first to see these cases in numbers, while those in the hinterland began to see a few cases only in 1938, and these came with extraordinary consistency from the coastal areas.

The classical keratitis superficialis punctata (Fuchs, 1889) which is usually sporadic and without striking conjunctival changes has been observed here as elsewhere for a long time. It is, however, sometimes forgotten that Fuchs described acute conjunctival

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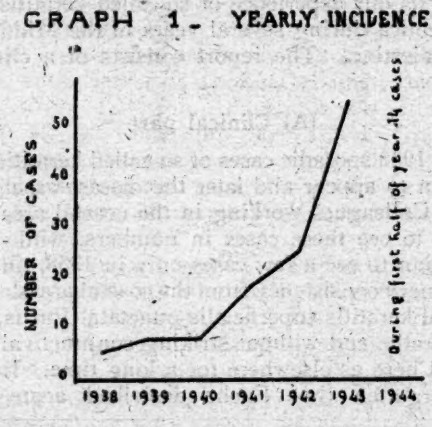
changes in this disease which at that time also seems to have appeared epidemically. It is noteworthy that three months before Fuchs' publication this keratitis arising from conjunctivitis had been described and named more correctly keratitis subepithelialis by H. Adler of Vienna (1889) who thus is the author to be credited with the first description of the disease.

In 1939 the first report appeared of an epidemic occurring in Palestine (Feigenbaum). It identified the condition with the epidemic kerato-conjunctivitis which had occurred during previous decades in the coastal towns of India: Bombay, Madras, Calcutta and in Batavia, as reported by Herbert (1901), Kirkpatrick (1920), Wright (1930), Zachariah (1930), Kirwan (1934), Westhoff (1912), and further expressed the opinion that the condition was in some way associated with the climate of the sea coast (and possibly with some kind of hypovitaminosis as a predisposing factor). The first two patients of A.F., who did not come from the coastal plain, were two children from Jerusalem whose father had brought them a pail of sand from Jaffa.

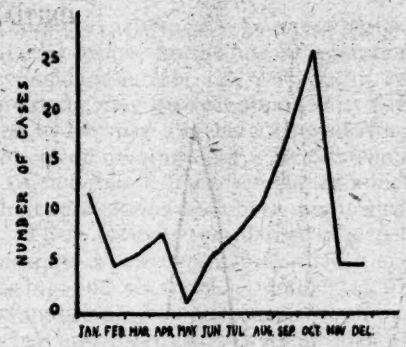
In the meantime a series of reports have appeared in Europe and North America in which there is a notable consensus of opinion that the condition is aetiologically associated with proximity to the sea. This opinion is expressed in the description "Shipyard-conjunctivitis" which has been applied to it (Sanders, 1942). In 1941 J. B. Hamilton described an epidemic of the disease in Tasmania where the majority of the cases also came from the coastal region.

The increasing incidence of the condition in this part of the world as well as a great number of cases among Polish cadets stationed



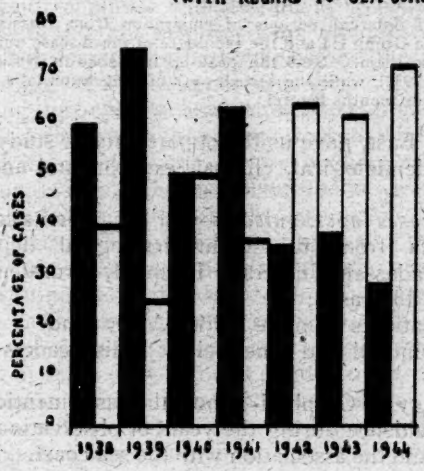
Yearly incidence of cases belonging to Group I. Note the rise.

GRAPH 2 - MONTHLY INCIDENCE.



Monthly incidence of cases belonging to Group I. Note the peak in the beginning of wet season.

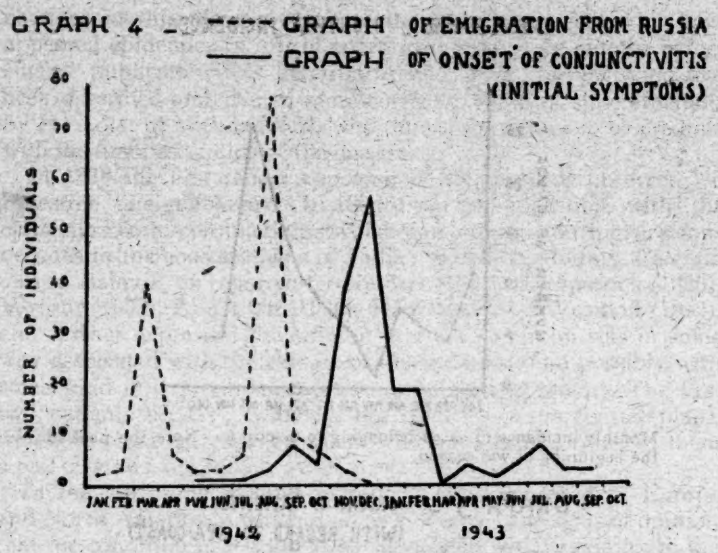
GRAPH 3 - ORIGIN OF PATIENTS (WITH REGARD TO SEA COAST)



■ PATIENTS FROM COASTAL REGIONS

□ PATIENTS FROM INTERIOR OF COUNTRY

Distribution of cases belonging to Group I according to their origin—with regard to coastal regions and inland (whether from the sea coast or from the interior of the country). Note the rise in percentage of the cases coming from the interior.



Relation of different periods of emigration from Russia of cases belonging to Group III and the incidence of the disease (initial symptoms among them. Note the peak of incidence in (November and December 1942), while the second peak of emigration falls on August (three to four months before).

in the Middle East, gave us the opportunity of studying the problem from epidemiological, clinical, experimental and histological standpoints.

Sources of cases investigated :—Our 381 patients consisted of :—

(1) Patients from the Ophthalmological department, the Rothschild Hadassah University Hospital, Jerusalem, and private practice, total 133 cases;

(2) Fifty patients from the British Army; and

(3) One hundred and ninety-eight Polish cadets already mentioned.

Epidemiology :—Graphs 1-3 show the cases mentioned in Group 1 and give incidence during the years of observation, the seasonal distribution, and the association with the sea-coast.

Graph 4 gives the seasonal incidence of the cases mentioned in Group 3. It can be seen from Graphs 2 and 4 that the beginning of the winter (in this part of the world the rainy season) is the special period for the epidemic incidence, while only sporadic cases were observed during the rest of the year. This is in complete agreement with the Indian and recent American reports which are very detailed in clinical observation (Hogan and Crawford, 1942).

While the source of the " first case " is not known, there is no

doubt that each case constituted a source of infection for susceptible contacts. Frequently members of one family were affected simultaneously.

The rôle of trauma in aetiology.—In our experience trauma such as corneal epithelial lesion, hordeolum or operation on the globe, plays a not inconsiderable rôle. A very slight epithelial trauma which can easily occur may give an opportunity for the entry of an ubiquitous virus which may also be conveyed from one patient to another by medical or nursing staff. In this connection mention may be made of two small house epidemics which occurred in patients on whom operations had been performed for cataract, glaucoma, etc. These patients complained of a feeling of pricking and of the sensation of a foreign body in the eye. During the change of dressing one observed a number of fibrinous threads between the lid margins. Smears and cultures did not show any bacteria. The lids and conjunctiva were swollen and in several of these cases the conjunctivitis was followed by a typical punctate keratitis. Bandaging did not interfere much with the healing of the condition. We particularly mention one case where a paracentesis of the cornea had to be done because of profuse bleeding into the anterior chamber with secondary glaucoma although a conjunctivitis, of the type just described, was present: no harm to the eye resulted despite the paracentesis and the repeated subsequent re-opening of the anterior chamber. This case was in hospital during the house epidemic already mentioned.

It is no wonder then that the reports from the United States indicate a strong incidence among factory workers, while the rest of the population in the same neighbourhood was only slightly affected. This indicates that slight lesions of the conjunctiva increase the susceptibility to the disease, and this justifies the ruling of the California State Industrial Accident Commission that disability resulting from the disease is subject to compensation (M. J. Hogan in discussion of paper of Bedell, 1943).

The incidence of the condition is affected by neither age (the age incidence of our cases varied from 4 months to 68 years), sex (both sexes were almost equally represented) nor social class. Certain conclusions regarding epidemiology may also be drawn from the experimental part of this report.

No indisputable instance of recurrence was observed in any of our cases, although exacerbations were seen especially in the very chronic cases found in Group 3.

Symptomatology.—It is difficult to estimate the incubation period which in our cases appeared to be between 5 and 14 days. As in all descriptions of this condition the subjective symptoms were prominent. The general condition of the patient was unaffected in the great majority of cases. The symptoms consisted

of pricking, itching, and/or the sensation of a foreign body in the eye and later sometimes of a slightly blurred vision indicating corneal involvement.

The objective findings were: lacrimation; swelling of the lids accompanied by pseudoptosis which involved mainly the outer 2/3 of the lid in 85 per cent. of Group 2; typical glistening of the conjunctiva (" cellophane surface appearance "), marked swellings of the conjunctiva of the lower lid which sometimes reached cockscomblike dimensions, swellings of the plica semilunaris and caruncle, and painful swelling of the pre-auricular gland often accompanied by swelling of the sub-maxillary gland. The pre-auricular glands were palpable in 90 per cent. of the cases in Group 2, but in some there was no accompanying tenderness, the gland appearing to remain palpable after the tenderness had gone. Especially notable was a delicate fibrinous thread-like secretion, such as is commonly found in spring catarrh. The secretion contained a few monocytes. No inclusion bodies were found in epithelial scrapings.

The condition began bilaterally (50·3 per cent. of our cases) or unilaterally (49·7 per cent.). In the latter there was no difference in the frequencies of affection of either eye (25·5 per cent. showed right eye affection and 24·2 per cent. showed left eye affection). In the course of a period varying from four days to several weeks the second eye frequently became affected. In it the conjunctival changes were usually less severe. In Group 3 where the condition was extremely chronic only two out of 198 cases remained unilateral.

The conjunctival changes described above must be considered as the basic manifestation of the disease. They are characteristic enough to allow a certain diagnosis even in the absence of corneal lesions, especially when occurring in epidemics and when conjunctival smears and cultures are negative. This applies to our cases where, moreover, conjunctival scrapings in an overwhelming proportion showed mononuclear cells and where no inclusion bodies were found.

The corneal lesions enter the picture very frequently as a kind of complication and are specific to such a degree that for quite a long period the name of the disease was derived from them.

The corneal changes presented themselves in three or four different forms:—(1) Ill-defined sub-epithelial dots ranging from tiny spots to small maculae (macular keratitis). This was the most frequent form. The number and distribution of these dots varied. These lesions in the cornea were located either mainly in the centre or in the periphery, and there were also mixed types.

(2) Superficial epithelial infiltrates some of which were vesicular and some of which stained with fluorescein.

(3) Disciform keratitis. This is the rarest form but is definitely a manifestation of the disease, as it may appear simultaneously with the typical dots in one or the other eye of the patient. The disciform infiltration accompanied by thickening of the cornea, with which there may be marked folding of Descemet's membrane and often keratic precipitates, recedes leaving several dots of opacity at various levels of the cornea which gradually fade away. 5·3 per cent. of our cases showed precipitates in Descemet's membrane.

Corneal changes were found in 60·4 per cent. of cases in Group 1. Of these, 22·5 per cent. had both eyes, 37·5 per cent. the right eye and 40 per cent. the left eye affected. In Group 3 the cornea was affected in 65·6 per cent. of cases. Of these 59·2 per cent. had both eyes, 13·8 per cent. the right eye and 27 per cent. the left eye affected. As far as one could judge the interval between the conjunctival changes and the keratitis was 7-17 days. There was no direct association between the severity of the conjunctivitis and the appearance of the keratitis.

The conjunctival changes gradually diminished after a few weeks while the corneal complications in most cases lasted a longer period, usually from a month to 2½ years. Blurring of vision caused by the subepithelial dots may be ascribed to two factors: the opacity as such and the irregular astigmatism caused by the dots even when they are subepithelial, as some of them elevate the epithelium to a varying degree. This can be seen at the slit-lamp where the anterior corneal band of the optical section appears in places slightly broken when the light is moved over the corneal surface and, still more distinctly, at the ophthalmometer where the images are distorted as usual in irregular astigmatism.

The gradual diminution in number and density of these opacities can be followed graphically. During the stage of subsidence the larger dots frequently presented the appearance of a well defined linear rim with a pale centre. In cases that have been over-treated the conjunctival changes may not only remain for a long time but can be aggravated in a striking fashion. This occurred among our cases of Group 3 as will be described later.

It is noteworthy that a certain number of our patients easily developed inflammatory changes in the palpebral skin (sometimes extending even to the cheeks) during the course of the disease. This dermatitis had the character of an allergic lesion provoked either by the tears or by some drug used.

Peculiarities of Group 3.—At the beginning of 1943 it came to the knowledge of one of us (A.F.) that there was a great number of trachoma cases among the Polish cadets, boys and girls between 12-18 years, stationed in Palestine. These cases constituted 10 per cent. of the total number of the 3,150 youths of Barbara Camp.

They had spent the end of 1941 and the whole of 1942 partly in Russia, partly in Persia at the shores of the Caspian Sea where they had gone (as can be seen by the data of Graph 4) after leaving Russia. They spent a variable time in Pahlevi and Teheran, whence they travelled via Iraq to Palestine. In many of the cases the precise date of onset of the disease is uncertain, but it is definite that the onset was not at the Caspian Sea but either in Teheran, Iraq or Palestine.

It appeared to us very doubtful whether these cases were true trachoma. The 198 cases detailed in this report (out of a total of 323 cases treated at Barbara Camp) were thoroughly re-examined with the help of the slit-lamp.

The clinical picture in the majority of the cases showed a great resemblance to trachoma as far as chronic gross papillary hypertrophy of the conjunctiva was concerned, but as one of the essential signs of the disease, namely pannus, was absent, the diagnosis had to be dismissed. There was in fact not a single case of trachoma in this group. The fibrinous discharge of the conjunctiva suggested a disease somewhat related to spring catarrh, but as only one case was found to be a true spring catarrh (with one typical limbal nodule), which was of course eliminated, and as a great proportion of the remaining cases showed the corneal changes of so-called epidemic superficial keratitis, it seemed most probable that this disease was the cause of the pathological changes in these cases.

The most striking feature of the cases in Barbara Camp was the great hypertrophy of the conjunctiva of both lids which was often very gross. This was frequently accompanied by a severe mucopurulent discharge which on bacterial examination gave a negative result. This unusual feature can be explained by the very drastic treatment given to these cases which as already mentioned were considered to be trachomatous. The treatment consisted of silver nitrate, copper sulphate, sublimate massage and in the majority of cases even expression which left very definite scarring. In this way the disease was maintained and healing prevented. A third of the patients showed chronic ptosis. More than three-quarters of the material used for experimental purposes was obtained from these patients.

Therapy.—There is more to be said negatively than positively under this heading. It seems clear that energetic treatment aggravates the condition. In this connection silver preparations are chiefly at fault as ophthalmologists so very enthusiastically turn to them in acute catarrh of the conjunctiva, but even other drugs used in conjunctivitis do more harm than good. It is not easy to say whether or not the heavy salts increase the disposition to keratitis as indicated in a personal communication by Dr. Levy-

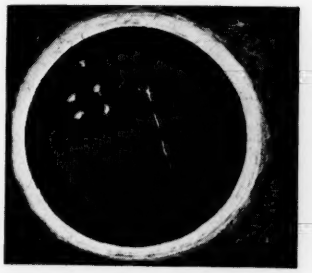


FIG. 1.

Subepithelial corneal changes six days after inoculation (Rabbit No. 193).

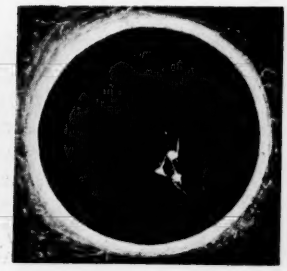


FIG. 2.

Corneal changes after four days (Rabbit No. 605).

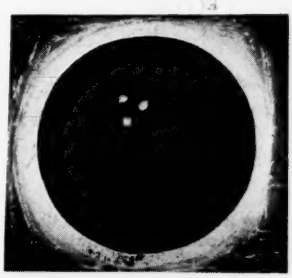


FIG. 3.

The same rabbit as in Fig. 2 six days after.

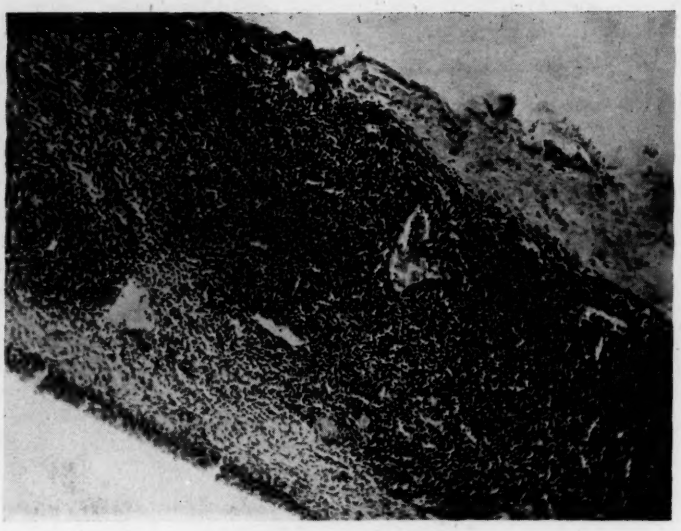


FIG. 4.

Section of conjunctiva *two days* after onset of the disease. Note oedema separating the epithelium from the marked subepithelial diffuse infiltration where pronounced capillary dilatation exists (Case 177; ×32).

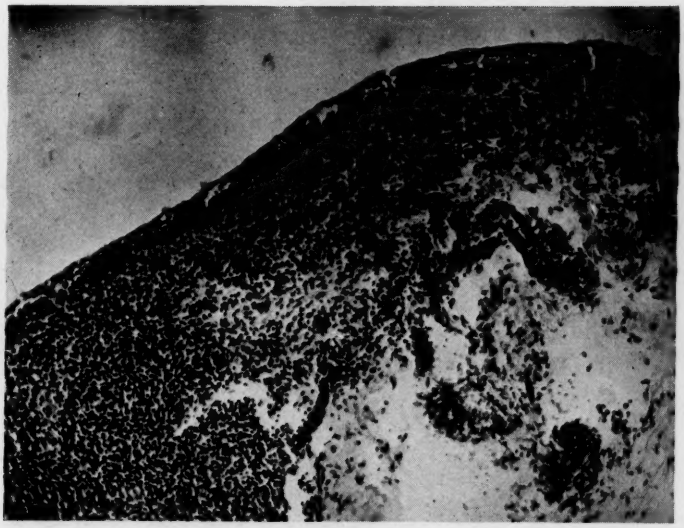


FIG. 5.

Section of conjunctiva *six days* after onset of the disease. The massive subepithelial round cell infiltration is everywhere in contact with the epithelium (Case 179; ×58).

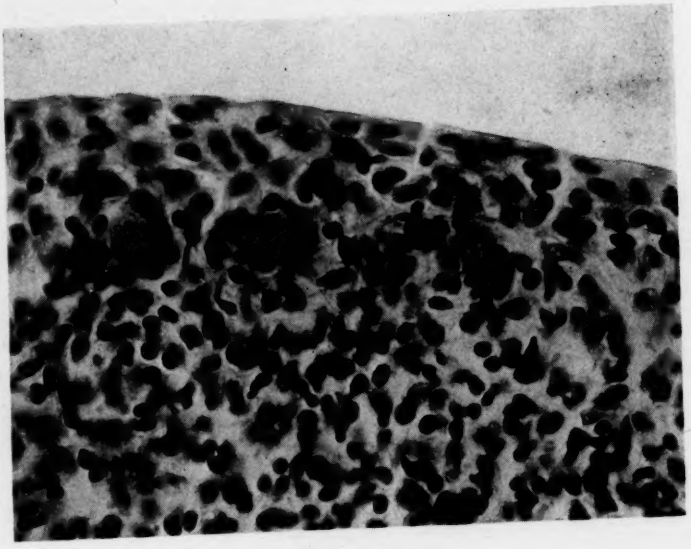


FIG. 6.

The same section as in Fig. 5 (×650) showing flattening of the epithelium.

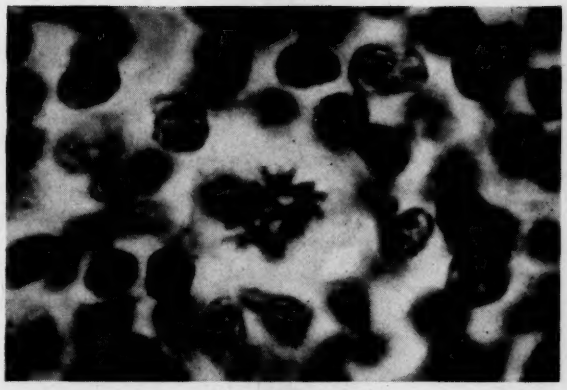


FIG. 7.

The same section as in Figs. 5 and 6 showing round cell infiltrate with one cell undergoing mitosis (×1800).

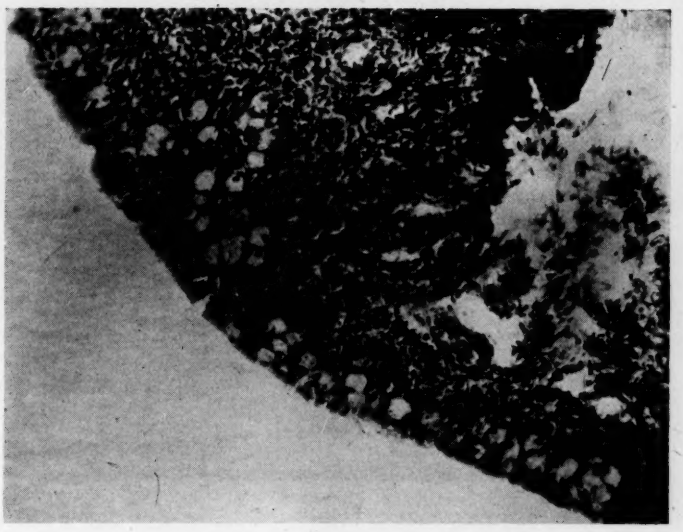


FIG. 8.

Section of conjunctiva *eighteen days* after onset of the disease. Epithelial changes with formation of goblet cells. Subepithelial round cell infiltration with admixture of polymorphonuclear leucocytes (secondary infection) as well as a moderate number of fibroblasts (Case 183; ×160).

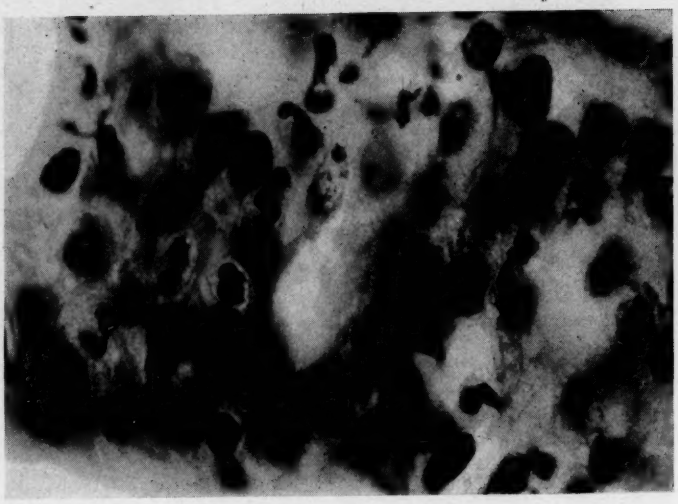


FIG. 9.

Same section as in Fig. 8 (×1350) also showing polymorphs (secondary infection).

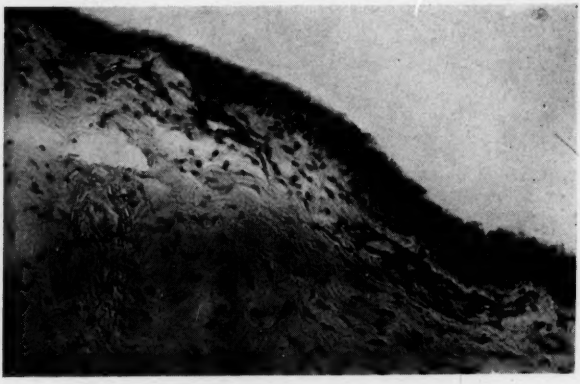


FIG. 10.

Section of a rabbit's cornea five days after successful inoculation. Portion containing the subepithelial macular lesions. Note the subepithelial bundles of elongated cellular elements. At one place these cells seem to intrude into the thinned epithelial cover (Rabbit No. 176, ×120).

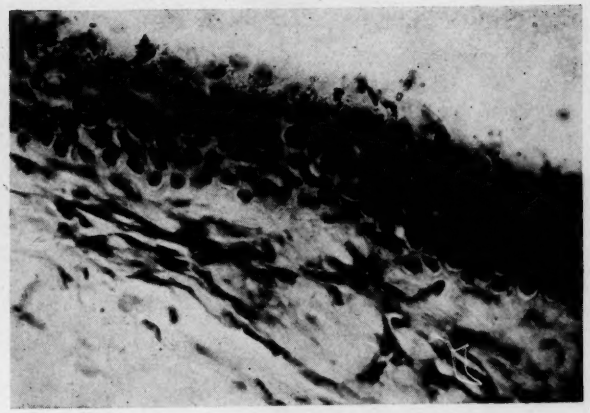


FIG. 11.

FIG. 12.

Sections of the same cornea as in Fig. 10. In the subepithelial layer the elongated mobilized cells form bundles. The cellular architecture of the epithelium is somewhat disorganised. The basal cells have lost their palisadelike arrangement and their nuclei—the normal perpendicular position. Note the detritus over the surface of the epithelium (× 350).

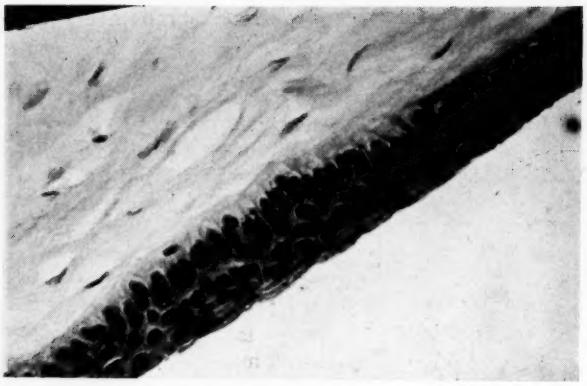


FIG. 13.

Normal portion of the same cornea. Note the normal arrangement of the epithelial cells (× 350).

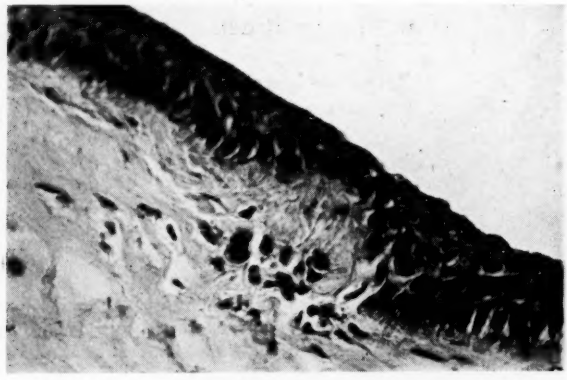


FIG. 14.

The mobilized cellular elements at one place seem to intrude into the epithelium where the latter is thinned and reduced to about 2-3 layers (× 350).

Wolff. These should in any case not be used as they undoubtedly aggravate the subjective and objective signs. The best remedies are the frequent instillation of concentrated adrenalin solution (1 in 4,000) and douchings with cool water. Cocaine is often useful and atropine should be used for the keratitis when ciliary injection is present. After the complete disappearance of the conjunctival changes 2 per cent. yellow oxide of mercury ointment, with 5 per cent. dionine, appear to be of use for the corneal infiltrations. Iontophoresis with sodium iodide was found to be of use in those cases of keratitis where the changes were confined to the epithelium, but had no effect where they were sub-epithelial. Treatment with immune serum is of theoretical interest and has been used by Braley and Sanders (1943) with good results in a small number of cases. Sulphonamide given locally or by mouth does not, in our experience, help the condition, except in cases with mixed infection where only the conjunctival condition may improve.

In a small series (6 cases) penicillin was tried, using 250 units to the c.c. as drops 2-hourly day and night for 3-4 days, without any effect whatsoever.

In a few cases of disciform keratitis intravenous injection of 1-3 c.c. of a 10 per cent. solution of sodium iodide seems to give rapid improvement and is recommended for such cases.

Differential diagnosis.—In the Middle East the following conditions must be considered :—

(1) *Acute conjunctivitis of the type of swimming bath conjunctivitis.*—In this condition there are likewise considerable conjunctival hypertrophy and swelling of the pre-auricular gland, but the sparse secretion contains polynuclear leucocytes and scrapings of the conjunctiva show inclusion bodies with varying frequency. There are no threads of fibrin and most cases tolerate treatment with silver and copper very well. There are no corneal complications.

(2) *Trachoma.*—Trachoma is often confused with the condition under consideration. Among the cases which Mulock Houwer described in 1937 as acute trachoma, three at least belong to the condition described here. Our cases in Group 3 showed an extraordinary similarity to the conjunctival changes found in trachoma. Yet these cases did not have the cardinal sign of trachoma—pannus, even after many months. The slit-lamp can best settle this point of differential diagnosis (Wilson, 1932).

(3) *Conjunctivitis vernalis.*—A certain resemblance exists in that threads of fibrin are found in both conditions. In the disease under study, however, there are not the typical conjunctival vegetations nor changes at the limbus. In spring catarrh the characteristic conjunctival changes mainly affect the tarsal conjunctiva of

the upper lid while the fornices are free and the lower lid in pronounced cases presents only a milky hue. In contradistinction our conjunctivitis shows the most important changes in the conjunctiva of the lower lid (glistening " cellophane surface appearance " and papillary swelling). Moreover the corneal changes found near the limbus in spring catarrh have an altogether different character.

(4) *Koch-Weeks' conjunctivitis.*—In this condition there are likewise acute swelling of the conjunctiva, fibrinous secretion and enlargement of the pre-auricular gland, but the fibrin is present in gross amount and contains numerous polynuclear leucocytes and Koch-Weeks' bacilli which seem to disappear after short treatment. Finally the corneal changes in Koch-Weeks' conjunctivitis appear simultaneously with the conjunctival changes and are of quite different type. Sub-conjunctival haemorrhages appear less frequently in kerato-conjunctivitis than in Koch-Weeks' conjunctivitis.

(5) *Herpes corneae.*—This is practically never bilateral. There are no conjunctival changes, inclusion bodies are found fairly regularly, and experimental inoculation of the rabbit's cornea is followed frequently by encephalitis. This did not occur in our animal experiments.

(B) Experimental part

Small pieces of conjunctiva removed under sterile conditions from the lower lid and placed in a small amount of physiological saline were used as our material. These small pieces of tissue were pounded up with sterile sand and the larger particles removed by centrifuging. The supernatant fluid obtained after this process was considered to be a suspension of the infective agent and its sterility was proved by inoculation on blood agar and in serum broth. In the experiments described below this suspension was used without waiting for the bacteriological findings. Naturally only the results obtained with bacteriologically negative suspensions are included.

From a series of investigations it became clear that the pieces of conjunctival tissue in saline kept in the refrigerator, contained the infective agent in active form for as long as one month. On the other hand the suspensions remained infective for only 2-5 days.

In some cases the experimental materials used were scrapings from the conjunctival epithelium. This method soon appeared to be inefficient and was abandoned.

Animal experiments

Rabbits.—Inoculation was carried out as follows: The cornea, which slit-lamp examination had shown to be free from opacities, was scratched with a fine hypodermic needle and the suspension

described above was rubbed into the scratches. In addition, 0·1 c.c. of the suspension was injected sub-conjunctivally and when possible into the membrana nictitans. For the success of the experiment it did not matter whether or not the membrana nictitans or the conjunctiva were inoculated. Inflammatory changes in the conjunctiva were minimal and non-specific in that they did not resemble the changes found in the human conjunctiva. As a control, one eye only was treated with the suspension and the other inoculated simultaneously with physiological saline.

Summary of positive results from inoculation experiments

Of the 33 rabbits in which one eye was inoculated with the suspension, 30 eyes showed typical changes in the sub-epithelial layer of the cornea in the form of opacities similar in appearance to those found in most cases of human so-called keratitis epidemica and described as punctate keratitis. (The material used for these 33 inoculations came from 25 cases of Group 3 and 8 cases of Group 1 of the three negative results two belong to Group 3 and one to Group 1.) Some albino animals were used for inoculation and contrary to the experience of Wright (1930) no differences in susceptibility could be established between melanic and albino rabbits.

These fairly regular takes in the rabbit's cornea showed the following aspect and course: After an incubation period of 24-48 hours, sub-epithelial corneal infiltrates could be seen in the form of thin lines which in places showed bulbous thickenings. After several days hardly anything could be seen of the lines while the thickenings presented the appearance of small opacities as described above (see Figs. 1-3). Although one case lasted for almost 3½ months these opacities remained visible for an average of two months. Towards the end of this period the opacities faded in the following way: A central clear area appeared in the opacity giving it the appearance of a ring which finally faded away.

In five cases an attempt was made to introduce the condition from an infected cornea to a healthy one in order to obtain passage of the infective agent. The lesions of the diseased cornea were removed under slit-lamp, and the material used on a second rabbit's cornea in the manner described above. In only two cases was a typical picture obtained. Of the others one was doubtful, two were negative. Attempts to passage the condition from the two positive cases were unsuccessful. It is noteworthy that the incubation period which was 1-2 days originally, increased to 4-5 days in the passage.

Mice.—Young mice (3-4 weeks old) were inoculated intracerebrally (0·03 c.c.) and intra-peritoneally (0·5 c.c.) by the method

described by Sanders (1942). In addition inoculation was carried out with infected membrana nictitans of rabbits, a method which has given good results with herpes virus, while other methods of inoculation with the latter are hardly effective in mice (Steigman and McNair Scott, 1942).

All these methods were consistently negative in their results. Fifty mice were inoculated without a single one showing any evidence of disease. In order to find out whether the infectivity of the agent could be enhanced by passage, 15 mice were sacrificed five days after inoculation, the brain removed with sterile precautions and after being pounded up was used for intra-cerebral injections into other mice. Even after five passages there was not the slightest evidence of pathological changes in the animals.

Likewise inoculation experiments were negative in mice which had previously been treated with X-rays (500 R) in order to diminish resistance.

Experiments with vitamin-deficient animals (riboflavin, thiamine) were likewise negative.

Similar experiments on mouse brain, using tissue culture material gave negative results.

Control experiments.—As mentioned above for the purpose of control and for the purpose of removing any doubt regarding the specificity of the corneal changes, the second eye of the rabbit was always inoculated simultaneously with saline. These inoculations produced no changes apart from fine lines of infiltration which disappeared in 2-3 days without leaving any trace. With the same object inoculation experiments were performed using normal conjunctiva as the inoculated material. Constant changes were obtained in these experiments similar to those obtained when pathological material was used—lines with bulbous thickenings at the crossings, but they disappeared in several days or at most one week. This is in contrast to our positive inoculation results in which the lesions in the form of a macular keratitis remained for at least a month and usually 2½ months.

Immunity.—The following neutralisation experiments were carried out to determine whether or not immune bodies were present in the serum of the convalescent case and whether specific neutralisation was possible.

Infective material from human conjunctiva and from tissue culture, as will be described below, was diluted (1 : 1) with physiological saline or with convalescent serum. One eye of the experimental animal was then inoculated with the suspension diluted with physiological saline, and the other with the suspension diluted with serum. In all six cases the typical pathological changes described above appeared in the eye which was inoculated with the suspension diluted with saline while the other eye showed

no more than the non-specific changes described above in the control experiments, and which disappeared at most after one week.

In a number of cases further infection was attempted on corneae of rabbits which had previously been inoculated with positive results. This was done during the period of full development of the disease, and shortly after the disappearance of the lesions. As no diminution in the susceptibility of the cornea was found in this experiment (both in active cases and those shortly after disappearance of lesions), no appreciable immunity could be detected in the affected tissue.

Tissue culture

In view of the negative results obtained in mouse-experiments, a series of experiments with tissue culture was initiated according to the method of Sanders (1943).

Technique.—The brain was removed from 12-15 days old mice embryos, cut into small pieces, and planted into Carrel flasks. The medium used consisted of 0·5 c.c. chicken plasma, 0·5 c.c. tyrode solution, 0·5 c.c. normal human serum and 3 drops of saline chicken embryo extract. The cultures were incubated at 37° C. Four days after incubation the tissue cultures showing an abundant cell outgrowth were inoculated with 2-5 drops of a suspension of the infective agent (prepared in the way described above) and left standing at room temperature for 5-7 days. For the purpose of passage the inoculated tissue culture was cut into pieces and the infected fragments were put into another Carrel flask containing embryonic brain culture. At each passage a piece of the tissue was pounded up and the suspension inoculated into a rabbit's cornea.

Results.—The first two cultures showed bacterial contamination after a few days' incubation, despite the fact that the blood agar and serum broth cultures had remained negative. The cultures remained sterile only when the precaution was taken later of washing the human conjunctiva with 1/4000 oxycyanate of mercury before removal of the tissue.

Using three affected conjunctivae as material, tissue cultures were infected and these were maintained to the 7th passage. All subcultures of these three series were inoculated on rabbits' corneae with positive results. As there is a dilution of 1 :10 with each subculturing, and therefore in seven passages a dilution of 1 : 10,000,000, it can be readily seen how much enhanced the agent becomes in tissue culture. These experiments show that here we most probably deal not only with maintenance of the infective agent but that a real multiplication of the latter had taken place. The original suspension of the agent, on the other hand, was infective only up to a dilution of 1 :20—and higher dilutions gave negative results.

Inoculation experiments on mice with tissue culture material, were completely negative and thus a neurotropic tendency could not be demonstrated. The infective agent was tested for dermotropic properties by inoculation into the skin of a number of patients during the initial, fully developed and chronic stages of the disease. In no single instance was a local reaction obtained.

Filtration experiments.—Pieces of tissue were taken from 12 Carrel flasks under sterile precautions, pounded up, suspended in about 15 c.c. of sterile tyrode, and lightly centrifuged. The supernatant fluid was passed through a Seitz filter. The filtrate was specifically infective for the rabbit's cornea in direct experiment and after transmission in tissue culture to the 4th passage.

These tissue culture experiments strongly suggest that the infective agent in the disease under consideration is a filtrable virus. Many examinations of the scrapings of the conjunctiva were made by us in a vain search for inclusion bodies. Major van Rooyen to whom we are greatly indebted was kind enough to examine at least 50 specimens which failed to show any inclusions.

Histology

Histology of human conjunctiva.—Histological examination of cases at the commencement and at the height of the disease gave fairly characteristic appearances. In all cases the conjunctival tissue examined came from the lower fornix. The tissues were fixed in Zenker's solution and stained with haematoxylin-eosin and diluted Giemsa solution. Sections show an early flattening of the cylindrical cells of the epithelium (Fig. 6). In the sub-epithelial tissue marked capillary dilatation and oedema are the outstanding features. The epithelium is thinned at first especially over places where the subepithelial tissue shows considerable infiltration and oedema, most probably as a result of mechanical pressure. Later on thickening of the epithelium accompanied by many mitotic figures occurs. During the first few days the diffuse subepithelial infiltration at many places appears separated from the epithelium by oedema (Fig. 4). Soon, however, the infiltration is everywhere in contact with the epithelium and presents a constant picture consisting almost entirely of two types, common lymphocytes and large histiocytic cells of epithelioid character (Figs. 5 and 7); the latter show numerous mitotic figures (Fig. 7). In an early case single eosinophils can be seen also in the subepithelial infiltrate and in later ones a varying number of polymorphonuclear leucocytes may be found scattered between the epithelium and the subepithelial tissue which may be considered as evidence of secondary infection (Figs. 8 and 9). In the later stages there is also a moderate perivascular infiltration.

As is common in chronic conjunctivitis one frequently notices epithelial changes with the formation of goblet cells, several of which conglomerate to form large detritus-containing crypts some of which open to the surface (Fig. 8). In very chronic cases showing strong papillary hypertrophy, there is a histological picture reminiscent of that of trachoma. Rows of epithelial cells seem to pass inwards, while the essential feature is a marked proliferation of the papillae towards the surface of the conjunctiva. Often with these changes the superficial epithelial cells are not only flattened but also disorganised, and in places reduced to a single layer.

Histology of a rabbit's cornea.—The cornea was examined histologically of a rabbit which had been successfully inoculated five days previously. The portion of the cornea containing the typical lesions (macular keratitis) presented the following changes :—

In circumscribed areas, beneath the epithelium a marked increase in numbers of elongated cellular elements is to be seen, originating either from the corneal corpuscles or from wandering cells. These cells are prominent, their cytoplasm is distinctly basophil and the nuclei are enlarged. Here and there they form short, more or less compact bundles (Figs. 10 and 11).

The epithelium above these spots has mostly lost its regular architecture. The cells of the basal layer lose their palisade-like arrangement and the nuclei change their position from perpendicular (Fig. 13) to the corneal surface to horizontal (Figs. 11 and 12). The epithelial layer is clearly thinned; in some places the mobilised cells seem to intrude into the epithelial cover and at such a bulge the epithelium is reduced to 2-3 layers (Figs. 10 and 14). It should be noted that the corneal surface over the subepithelial lesions described is slightly irregular and covered with some detritus, resulting from the incompletely healed mechanical injury produced at the time of inoculation (Figs. 11 and 12). (No relation can be established to Bowman's membrane as this membrane is non-existent in rabbits.)

Comment

There are no doubts concerning the specificity or the infectivity of the disease under consideration. The mode of infection is not known although predisposing circumstances for infection can be recognised such as trauma and climatic conditions.

A whole series of facts suggest that the inciting agent is a filter-passing virus. Examinations of direct smears and of cultures failed to reveal any bacteria.

Experimentally secretion from the conjunctiva did not produce the disease, while conjunctival tissue direct or after tissue culture gave positive results. In the absence of bacteria the material remained infective; this can be explained only by active propagation of the infective agent within the living cell.

The neutralisation experiments were indicative of the presence of immune bodies in human convalescent serum. The clinical fact of non-recurrence of the disease seems to indicate that in man it is followed by immunity. On the other hand it is noteworthy that (1) the presence of lesions on the rabbit's cornea and (2) the subsidence of these lesions seemed to confer no immunity to the cornea in the rabbit. This might be explained by the fact that in the rabbit, unlike in man, the disease is confined to the cornea, the conjunctiva is not affected and presumably no general immune reaction with production of antigens occurs. This point, however, requires further investigation.

Pathological findings in the keratitis under discussion are scarce and inconclusive. The changes found histologically in a rabbit's cornea are interesting. It is of course not permissible to draw conclusions on the specificity of these changes from this one case. Should, however, the changes prove to be due to the specific agent, this finding would acquire importance in that it is illustrative of the earliest changes occurring in this form of human keratitis. The reversibility of the latter process, *i.e.*, the gradual disappearance of the macular lesions in the course of recovery, might then find an explanation in the assumption that the elements of infiltration, the mobilised cells, which do not form scar tissue regress gradually without leaving any trace.

Changes in the virulence of the disease in the course of epidemics are reported from time to time. The protean appearance of the corneal lesions in particular induced Wright (1930) to suggest the name keratitis diversiformis for the disease. In Palestine, too, some change in the appearance of the corneal lesions could be observed. While in the beginning epithelial alterations such as minute vesicles and subsequent epithelial defects taking fluorescein stain were in the majority, in the past few years mostly subepithelial macular lesions or even deeper-seated ones were seen. This may possibly be due to multiple passages in the course of time.

In this connection the immense spread of the disease since the end of the thirties may be recalled. The movements of populations before and to a far greater extent during the war naturally suggest themselves as factors in the spread of the disease.

Summary

(1) Three hundred and eighty-one cases of kerato-conjunctivitis were investigated in the Middle East, chiefly from Palestine.

(2) The majority of these cases occurred during epidemics.

(3) In the Middle East the beginning of the rainy season appears to be the period of maximum incidence of the disease.

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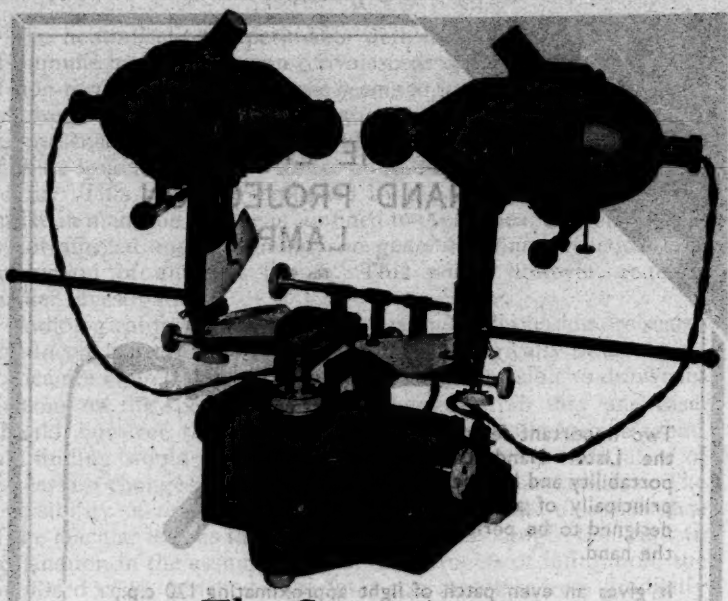

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(4) In Palestine the disease although now occurring inland, first manifested itself in the coastal plain. This is in accordance with findings in other parts of the globe.

(5) In some cases trauma appeared to play a definite rôle in determining the onset of the condition.

(6) The affection of lids, conjunctiva, regional glands and cornea formed a well defined clinical picture differentiable for the most part on clinical grounds from swimming bath conjunctivitis, spring catarrh, trachoma, Koch-Weeks conjunctivitis and herpes corneae.

(7) In 60·4 per cent. of cases the cornea was involved.

(8) The relevant cases free from corneal lesions were diagnosed from the clinical picture, the absence of bacteria, typical smears and the occurrence during epidemics.

(9) The mildest therapies proved the best. Douchings with cool water, instillation of adrenaline and, if necessary, cocaine and atropine drops were the most satisfactory remedies. Energetic treatment prolonged the disease and caused gross changes in the conjunctiva.

(10) Histological examination of human conjunctiva showed flattening of the epithelium, marked capillary dilatation and oedema in the subepithelial tissue and subepithelial infiltration with lymphocytes and large mononuclears, multiple mitoses and, in chronic cases, marked hypertrophy of the papillae.

(11) Histological examination of a rabbit's cornea in one case of inoculation keratitis showed notable changes.

(12) Experiments with rabbits confirmed the specific infective nature of the causal agent.

(13) This agent was not infective for mice by different methods of inoculation.

(14) Tissue culture and filtration experiments showed that the infective agent is a filtrable virus.

(15) Clinical immunity was apparently present in all of our cases; this was not found in experiments on the rabbit's cornea. Immune bodies were shown to be present in the blood of convalescent human cases.

Conclusion

Epidemic kerato-conjunctivitis is a specific disease of the conjunctiva and cornea caused in all probability by a filter-passing virus which can produce a similar condition in the cornea of the rabbit.

It has its own well defined epidemiological and clinical features.

Treatment must not be energetic. Douching with cool water and instillation of adrenaline and, if necessary, cocaine and atropine drops are the most helpful remedies.

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THE AETIOLOGY OF TRACHOMA*

A critical review of present knowledge

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AT the present time, only two theories of the aetiology of trachoma are generally accepted, the virus theory and the rickettsial theory. I believe that these two theories are not mutually incompatible but can be reconciled. The conflict is indeed one of nomenclature rather than of fact and largely depends on what we choose to call a rickettsia and what we choose to call a virus. The evidence so far accumulated leads to the conclusion that trachoma is a specific infectious disease, not caused by any cultivable bacterium, but due to a filter passing agent which is almost certainly identical with the elementary and initial bodies found in the inclusion bodies (Prowazek-Halberstaedter inclusions). Further, I shall attempt to show that the evidence that any rickettsial body other than these elementary and initial bodies is the cause of trachoma is inacceptable and shall discuss the relationship of these bodies to the viruses and the rickettsiae. Since much of the evidence to be presented is dependent upon experiments in animals and since there is some reason for doubting the validity of such experiments, it will be necessary to discuss this question first.

I.—The validity of animal experiments in trachoma research

It is now generally accepted that trachoma can be conveyed only to apes and monkeys and that other animal species are insusceptible. The disease produced by inoculation in apes and monkeys is not identical with that in man. The usual criterion adopted in these animals has been the production of a crop of follicles on the conjunctiva. Wilson[1] has drawn attention to the following characteristics of this reaction.

1. *Inclusion bodies are very rarely found in conjunctival scrapings.*—There is only one report[2] of their being found in any species of monkey. In apes they have been reported more often but still only rarely.

2. *No follicles are ever formed on the tarsus,* they occur only in the fornices.

* Received for publication, October 26, 1944.

3. *There is no vascularization of the cornea.*

4. *There is no subsequent scarring of the conjunctiva.*

Now in man, the presence of inclusion bodies, the formation of follicles on the tarsus, vascularization of the cornea and scarring of the conjunctiva are the four cardinal diagnostic signs of trachoma. Their absence in monkeys therefore casts doubt on the claim that trachoma can be conveyed to these animals. In the case of the *Macacus rhesus*, Julianelle[3] has made a careful examination of the follicular reaction and has shown that it is specific for trachoma and cannot be produced by inoculation of material from other types of folliculosis, nor by viruses, bacteria or chemical agents, but until recently no one had attempted the critical test of inoculating material from experimental trachoma in monkeys into human volunteers. This has now been done using the grivet monkey (Lasiopyga griseoviridis)[56], and it has been established that the grivet monkey is susceptible to trachoma, in spite of the fact that it does not show the four cardinal signs. Further, it is established that the virus multiplies in the grivet up to at least four passages and that material from the fourth passage in the grivet is infective for man.

If this were the whole story the position would now be most satisfactory, but unfortunately a further complicating factor enters into the situation: the occurrence in monkeys of a spontaneous folliculosis. A spontaneous non-trachomatous follicular disease of the conjunctiva is not uncommon in man and many other animals. Nicolle and Lombroso[4] have reported it in rabbits, chimpanzees and lower monkeys. Wilson[1] describes it in grivet and rhesus monkeys and a chimpanzee. Julianelle[3] also mentions it (presumably in the rhesus) in describing his experiments on the specificity of the trachomatous reaction. Recent observations have shown[56] (1) that wild grivet and vervet (Lasiopyga griseoviridis and pygerythra) and other monkeys, freshly arriving in Cairo from the Sudan and Central Africa, may already have the disease, (2) that it may develop spontaneously, within six weeks of their arrival, in every one of a batch of grivets and young baboons (Papio hamadryas) kept in captivity[57], (3) that while the number of follicles is usually less and their situation not the same as in a typical trachomatous reaction, nevertheless in approximately one-third of the cases the disease is indistinguishable from a reaction to inoculated trachoma. I, therefore, consider that we should not accept a reaction in any species as trachomatous unless it passes examination by at least one of the following tests:—

1. It reproduces the four cardinal signs of trachoma described above.

2. It is shown by the methods used by Julianelle[3] in the case of M. rhesus that the reaction is specific for trachoma.

3. It is proved to be trachoma by inoculation into human beings with the production in them of typical trachoma.

Should only condition 1 or 2 be fulfilled it must also be known that the reaction does not occur, or only very rarely occurs as a spontaneous disease in the species under examination. Further, it seems that the grivet (Lasiopyga griseoviridis) in spite of its proved susceptibility to trachoma, the vervet (L. pygerythra) and the baboon (Papio hamadryas) are unsuitable for trachoma experiments because they too frequently suffer from spontaneous folliculosis. Experiments in which they have been used must be disregarded. The M. rhesus I have not myself had an opportunity of studying. Dr. R. P. Wilson, in a personal communication, tells me that he found spontaneous folliculosis less frequently in the rhesus than in other species. Julianelle[3] in his careful studies of trachoma does not mention it as a serious complication of his experiments. Therefore, it appears that we may tentatively accept *positive* results in the rhesus but I would urge great caution in accepting conclusions based on *negative* results. Julianelle[3] has shown that only about 50 per cent. of these monkeys are susceptible to trachoma. In such a case, if we use four animals for a test, there is only a 21 to 1 chance against all four animals failing to react even when a fully virulent inoculum is used. With six animals, the odds rise to 80 to 1, with nine to 369 to 1. Therefore, negative results in rhesus monkeys should not be accepted unless at least six or more animals have been used.

These facts must be kept in mind when assessing the value of any report of experimental work on trachoma.

II.—Trachoma is a specific infectious disease

This is now undoubted. Wernicke first proved it in 1823 by inoculating men with excised follicles from a patient of 2½ years standing. Since that time, similar experiments have repeatedly been performed and it is now certain that inoculation of trachomatous material in healthy human beings will produce trachoma. Julianelle[3], reviewing the literature, records that 108 volunteers have been inoculated of whom 73 became infected—a 63 per cent. positive result. He considers the failures due (1) to material for inoculation having been taken in a late, non-infectious stage of trachoma, (2) to resistance of the individual, for in some cases a person has succumbed to infection only after repeated attempts. Such transference of disease from one person to another is only explicable on the basis that the material inoculated contains an infectious agent.

III.—The infectious agent is not a cultivable bacterium

In the past, a very large number of different species of bacteria have been described as the cause of trachoma (*vide* Julianelle[3]). Their very variety casts doubt on their claims. Furthermore, no cultivable bacterium has yet been shown to produce trachoma when experimentally inoculated into man. *Bact. granulosis* described by Noguchi[5] as the cause of trachoma is no exception to this rule. Seventy-four attempts to infect man with cultures of this organism have now been reported. All but two have failed. In these two, the volunteers had both previously suffered from trachoma. Since healed trachoma is capable of acute recurrence, these two positive results are inacceptable. Comparing this with the comparative ease with which tissues from trachoma will reproduce the disease, it is obvious that the agent of trachoma has not been cultivated.

IV.—The infectious agent is filterable

It must be admitted that, in the majority of experiments made to demonstrate the filterability of the virus of trachoma, filtrates have been non-infective even when the original material before filtration has been proved infective. The number of successful filtrations reported is very small indeed. This, however, is one of those cases where one well controlled positive result may legitimately be held to outweigh a large number of negatives for the following reasons: (1) In all filtration work on viruses it is well known that adsorption by the filter plays an important part. Filtrates always show a lower potency than the original material filtered. Where this material is rich in virus, it is able to satisfy the adsorptive capacity of the filter and yet allow some virus to pass. When, however, the material has a low virus content, the filter may remove the whole of it and allow none to pass. In the case of trachoma we are dealing with tissues which do not have a high content of virus and moreover we cannot obtain material in large quantities. The richest suspensions we can prepare contain much less virus than the average suspension prepared from tissues infected with such a virus as vaccinia; (2) Reasons will be given in the next section for believing that the virus of trachoma consists of the initial and elementary bodies which form the inclusions. These initial and elementary bodies are found much more rarely outside the cells than is the case with the similar bodies found in inclusion blennorrhoea and psittacosis in both of which diseases filtration is more easily accomplished than in trachoma. The epithelial cells, which contain the trachoma inclusions, are themselves too large to traverse filters and unless in preparing

our suspension for filtration a large number of the inclusion bearing cells are ruptured, the amount of virus present in the form of free elementary bodies, that is in a form in which it is capable of being filtered, will be considerably less than would be thought from a titration of the infectivity of the suspension. It is probable that the ordinary method of preparing suspensions by grinding the tissues in a mortar does in fact leave many of the cells unruptured.

Bearing in mind then these two facts, the adsorptive capacity of filters, and suspensions with a low content of trachoma virus in a filterable form, we should expect most attempts at filtration to fail. The positive experiments must therefore be accepted as proof of the filterability of the virus if they pass scrutiny from other points of view. Let us examine them:

(*a*) *Filtration through filter candles.*—Bertarelli and Cechetto[2-6] infected one Macacus cynomolgus with a filtrate from a Berkefeld candle. Nicolle, Cuénod and Blaizot[7-8] infected one M. inuus and one chimpanzee with a filtrate from a modified Berkefeld candle. Since the trachomatous reaction in these three species has not been proved to pass any of the three tests demanded in Section 1 of the article, these experiments must be discarded as inconclusive. This leaves three reports of successful infection of M. rhesus. Julianelle and Harrison[9] report a single positive experiment where three out of six M. rhesus were infected with filtrate through a Berkefeld V candle. The original material was infective, the filtrate was bacteriologically sterile. The experiment was, therefore, well controlled and must be accepted.

Julianelle[3] further reports two experiments in which filtrates from Berkefeld V candles infected two out of four and one out of four M. rhesus. The original material was infective, the filters were tested with cultures of B. prodigiosus. These experiments must also be accepted.

Olitsky, Knutti and Tyler[10] report one experiment in which one M. rhesus out of three was infected with filtrate from a Berkefeld V. filter. The original material was doubtfully positive. The filters were controlled by filtration of B. prodigiosus both before and after filtration of trachoma. This experiment is also trustworthy.

(*b*) *Filtration through collodion membranes.*—Collodion membranes are considerably thinner than filter candles, and in the hope of reducing the factor of adsorption some workers have used them. Some experiments of Stewart[11] show, however, that a collodion membrane may have a considerable adsorptive power, and in point of fact attempts to filter trachoma through such membranes have been less successful than those with filter candles. Let us examine the positive claims.

Stewart[11, 12] reports three well controlled experiments where filtrates from filters impervious to B. prodigiosus were infective for animals. The animals used were grivets and baboons. Since we now know that these animals are very prone to spontaneous folliculosis we cannot accept Stewart's findings which may possibly have been falsified by the occurrence of this disease.

Thygeson and Proctor[13] report three successful filtrations. The filters were controlled against passage of bacteria by cultures of the filtrates, which were negative. The animals used were African Sphinx baboons which the authors had found uniformly susceptible to trachoma. As Stewart[58] has said, there are no records of the frequency of spontaneous folliculosis in these animals and the reaction in them has not been shown to pass the tests here demanded. Until it has, these experiments must also be discarded on strict critical analysis.

There remains a single, but admirable, experiment by Thygeson, Proctor and Richards[14] in which a filtrate from a collodion membrane of A.P.D. 0·6 μ, inoculated into the eye of a human volunteer, produced typical trachoma with inclusion bodies and free elementary bodies in large numbers. The original material was not tested for infectivity but contained inclusion bodies. The filtrate was bacteriologically sterile and contained elementary bodies. Discs cut from the same collodion sheet as the membrane were impermeable to *Bacterium granulosis* and *H. influenzae* but passed elementary bodies of molluscum contagiosum. This well controlled experiment is eminently acceptable.

To sum up then we are left with four trustworthy experiments in the M. rhesus and one in man. If we accept the results in M. rhesus, as I think we may, this series of successful filtrations should be considered to prove the filterability of trachoma. If, however, we reject results in the rhesus we are left with the single experiment of Thygeson, Proctor and Richards which, excellent as it is, requires repetition in order to put the matter beyond doubt.

V.—The relationship of the inclusion bodies to the infective agent

In the case of most other viruses which form elementary bodies (E.B.s) these have now been accepted as being the virus itself. Furthermore, in the case of some viruses, *e.g.*, fowl-pox, psittacosis, vaccinia, ectromelia of mice, the inclusion bodies are composed of masses of these elementary bodies. The occurrence in trachoma of both free E.B.s and inclusion bodies composed of them, taken with the evidence that the agent of trachoma is

filterable, is itself strong *prima-facie* evidence that the E.B.s of trachoma are the infective agents. We shall find that the evidence for this hypothesis consists of two parts: (1) Direct evidence; (2) Evidence from analogy with other viruses.

(1) *Direct evidence that the E.B.s and Inclusions of Trachoma are the causal agents.*—(*a*) It is well known that inclusion bodies are found more frequently in the early acute stages of trachoma than in the later more chronic stages. The most conclusive single demonstration of this is that of Julianelle[15] but in his review of the literature[3] he shows that it has repeatedly been observed by others. In studying inoculated trachoma in two human volunteers, Bland[56] also found inclusions most numerous at the very onset of the acute infection, thereafter their numbers decreased as the disease passed into its chronic stage. This is precisely what we should expect if the inclusions contained the infective agent.

(*b*) Inclusions are constantly present in the acute phase of trachoma if sufficient care and trouble is taken in searching for them.[16 17]

(*c*) Inclusions similar to those of trachoma are never found in normal human eyes or in any human ocular disease except inclusion conjunctivitis (inclusion blennorrhoea and swimming bath conjunctivitis) and in ocular lymphogranuloma inguinale both of which conditions have been proved to be due to viruses related to, but distinct from, trachoma.

(*d*) Julianelle[15] has shown that trachomatous tissues containing inclusions possess approximately twice the infectivity for M. rhesus of tissues in which inclusions cannot be demonstrated. Mixtures containing approximately equal amounts of tissues with and without inclusions have an infectivity approximately half way between. The infectivity of tissues is thus closely related to the presence of inclusions.

(*e*) The inclusion body is almost certainly not an artefact. The idea that virus inclusions in general are non-specific formations produced by nuclear extrusion, nuclear or cytoplasmic degeneration, phagocytosis of cell débris or bacteria, has been repeatedly put forward but is not now accepted by most virus workers. That it is untrue for the inclusion of trachoma is made probable by the work of Rice[18] showing that the matrix of the inclusion body is a carbohydrate which stains differently from the nucleus and cytoplasm of the cell and from phagocytosed bacteria and therefore cannot arise by phagocytosis of bacteria or cellular débris.

Summing up then we find that the inclusion is a formation *sui generis* especially associated with the acute phase of infection,

constantly present in trachoma, not found in other ocular conditions, closely related to infectivity. Almost certainly it contains the infective agent.

(2) *Evidence from analogy.*—Three other viruses are known which are closely related to trachoma morphologically, inclusion conjunctivitis, psittacosis and lymphogranuloma inguinale. In all these elementary and initial bodies occur and inclusions are found composed of elementary bodies, of initial bodies and of various mixtures of the two embedded in a more or less homogeneous ground substance or matrix. The inclusions of inclusion conjunctivitis cannot be distinguished from those of trachoma. Those of lymphogranuloma are similar but not identical. Many types of psittacosis inclusions are indistinguishable in ordinary specimens from those of trachoma though iodine staining by the method of Rice[18] reveals a difference in the composition of the matrix. For psittacosis, the evidence is now complete that the elementary bodies are the infective agent since suspensions of them are specifically agglutinated by, and fix complement with, psittacosis anti-sera[19]. The work of Bedson and Bland[20] and Bland and Canti[21] has shown that those inclusion bodies which are composed of masses of elementary bodies are derived from the other forms of inclusion by a process which they describe as a developmental cycle, the initial bodies forming the small, young, inclusions multiplying in number and reducing themselves in size until the large colonies of E.B.s are formed. That a similar cycle occurs in lymphogranuloma inguinale has been shown almost as conclusively as for psittacosis[22, 23]. Less conclusive but still very suggestive are Thygeson's[24] observations on a similar cycle in inclusion conjunctivitis.

Where such a close morphological similarity exists it seems reasonable to conclude that the inclusions of trachoma also represent colonies of the infective agent. The argument may be advanced that we must not trust too implicitly to morphological similarities since things which look alike are not always the same. Fortunately, we now possess evidence from the work of Rake and his colleagues[25] on complement fixation that these viruses are also related antigenically. This second coincidence so strongly supports the argument from morphological similarity that we can scarcely doubt its validity. The conclusion seems unavoidable that the inclusion bodies of trachoma are colonies of the infective agent.

Conclusive proof of this hypothesis could only be obtained:—

(1) By reproduction of the disease with purified suspensions of elementary bodies. It seems unlikely that such suspensions will be made so long as we have to use material from the human conjunctiva.

(2) By inoculation of isolated, washed inclusion bodies. This has been achieved in fowl-pox[26] and might be achieved in trachoma though the technical difficulties would be much greater.

(3) By cultivation of inclusions through several passages in tissues-culture with proof of infectivity of the later subcultures. This has been attempted by many workers[3, 27, 28, 29]. Of these, only Polef[30] claims to have been successful in cultivating the inclusions but has not succeeded in proving their infectivity. Therefore, his experiments do not advance the matter.

VI.—The Rickettsial theory of trachoma

This hypothesis has been put forward in two forms: (1) That rickettsial bodies can be demonstrated in trachomatous tissues which are the cause of the disease and are distinct from the initial and elementary bodies; (2) That the initial and elementary bodies are the cause of trachoma and are themselves rickettsiae and not virus bodies. These two variants of the rickettsial theory are confused by some but it is essential we should examine them separately.

(1) *A rickettsia, other than the initial and elementary bodies, is the cause of trachoma.*—The proponent of this idea is Busacca[31, 32, 33, 34], who claims to have found in conjunctival epithelial cells and in cells from conjunctival follicles, minute bodies which, from their staining reactions and morphology he considers to be different from the elementary bodies and to be similar to rickettsiae. Similar bodies could be found in the cells of the tunica vaginalis of guinea-pigs inoculated with trachomatous material. He himself[34] considers that "the researches are too recent and too few as yet to permit the drawing of definite conclusions." Busacca's ideas at first received support from Cuénod and Nataf[35, 36, 37, 38, 39] but later[40] these authors appear to think that the rickettsiae and the elementary bodies are one and the same. They have thus joined those who support the second variant of the rickettsial theory. Now[41] they have departed still further from their original position and consider that, while trachoma ranks near the rickettsiae some characteristics of which it possesses, it nevertheless differs from them in other respects.

Busacca's findings have been criticised by Thygeson[42] and by Braley[43]. The first was unable to find any rickettsial form except the elementary bodies in conjunctival cells and none at all in follicular material. In slides sent him by Busacca and by Cuénod and Nataf he was unable to find any true rickettsiae but only granules of a non-specific kind. Bengtson, to whom Thygeson submitted the slides, and who was at that time working with

rickettsiae, confirmed Thygeson's findings. Braley[43] demonstrated that the mitochondria and keratin granules of normal conjunctival cells can be stained by Giemsa and considers the bodies photographed by Busacca are undoubtedly these rather than rickettsiae.

There is general agreement as to the existence of the granules described by Busacca, Cuénod and Nataf but a divergence in the interpretation of their nature. While the evidence for the elementary and inclusion bodies as the infective agent is so strong we cannot accept Busacca's theory unless much more evidence can be found in its favour.

(2) *The elementary and initial bodies are rickettsiae.*—We have seen that Cuénod and Nataf[40] have come round to the idea that the rickettsiae described by Busacca and themselves are identical with the elementary bodies forming the inclusions. Polef[44] has also given strong support to this idea on the grounds of certain observations of his own on tissue cultures. The chief advocates of this theory are, however, Foley and Parrot[45, 46]. These authors do not advance any experimental evidence in support of their view but their work consists of a careful morphological comparison of the elementary, initial and inclusion bodies of trachoma with the rickettsiae of various diseases. They point out the close tinctorial similarities between the trachoma bodies and the rickettsiae and the tinctorial differences between trachoma and certain of the accepted visible viruses such as vaccinia and herpes. They further show that in certain rickettsial diseases intracellular formations very similar to trachoma inclusions occur. These similarities extend also to the viruses of inclusion conjunctivitis, lymphogranuloma inguinale and psittacosis and therefore these viruses are also classed as rickettsiae by Foley and Parrot. The question thus becomes one of the taxonomic position of this whole group and as such will be considered in the final section of this review. As against the conclusions of Foley and Parrot stands an equally careful morphological comparison of trachoma with the typical rickettsiae of typhus, Rocky Mountain spotted fever, Q fever and nine mile fever made by Bengtson[47]. She concludes that "morphologically the inclusion is rather distinct from the rickettsiae."

There remain to be discussed two further pieces of evidence which favour the rickettsial theory. The alleged occurrence of a positive-Weil-Felix reaction in trachoma and the evidence for transmission of trachoma by lice.

(3) *The occurrence of a positive Weil-Felix reaction in Trachoma.*—The first suggestion that the Weil-Felix reaction might be positive in trachoma came from Derkač[48]. Since then many authors have reported on this subject, some claiming that

the test is significant and of diagnostic value, others denying that it is more often positive in trachoma than in a representative sample of the normal population. Even those who claim positive results do not claim that the titre rises above 1/100 in the majority of cases. Surely such evidence does not warrant the conclusion that trachoma is a rickettsial disease. The subject has been well reviewed by Bengtson[47] and by Polef[49].

(4) *The transmission of trachoma by lice.*—Cuénod and Nataf, in a series of publications[38, 40, 50, 51, 52], claim to have shown that the granules found by them in trachomatous tissue can multiply in the body-louse when the material is inoculated per anum. Rickettsiae are found in the intestines of the inoculated lice and their ground-up bodies cause experimental trachoma even after six successive passages in lice. In the majority of these experiments the test object was M. inuus which has not yet been shown to pass the necessary tests demanded by this review. Strictly, therefore, these results must be rejected. On one occasion, however[40], ground lice containing rickettsiae infected a human being and this must be accepted as proving that the lice were infective. Trapezontzewa[53], in a scholarly critique of these experiments, supported by an experimental study of her own, shows that Cuénod and Nataf have not excluded the possibility that the cultivated lice used by them were infected with naturally occurring rickettsiae, for if batches of apparently healthy lice, in which rickettsiae cannot be found, are ground up and used as inoculum for further lice, spontaneous rickettsiae appear in the second or third passage. She could not confirm the infectivity of lice infected with trachoma material. Weigl[54] also has been unable to confirm Cuénod and Nataf's experiments and denies their statement that R. rocha-lima is the causative agent of trachoma since he could detect no agglutinins against this rickettsia in the sera of trachomatous patients even when these had a relatively high titre for proteus OX19, OXK and R. prowazeki.

In view of these criticisms we cannot accept Cuénod and Nataf's claim that rickettsiae from trachoma multiply in the louse and are the cause of the disease. The most that they can legitimately claim, on the basis of their experiment in man, is that the agent of trachoma may survive in the louse and retain its infectivity. No evidence has yet been produced that in nature lice are vectors of the agent of trachoma. Stewart[11] has indeed produced evidence which bears against it. 173 Pediculus capitis from 15 children with early trachoma and 379 P. corporis from similar cases were used to infect three baboons. No trachoma resulted but the number of animals used is too small for the result to be significant.

VI.—Discussion

In the course of this review we have seen that the available evidence shows that trachoma is an infectious disease caused by a non-cultivable, filterable agent, identical with the elementary and initial bodies found in the Prowazek-Halberstaedter inclusions, and bearing a close natural relationship to the viruses of inclusion conjunctivitis, lymphogranuloma inguinale and psittacosis. There is no evidence that this agent possesses an arthropod host, nor that the louse is a vector of the disease though the agent may survive for some days in the body of the louse. In what group of organisms are we to place this agent along with the three other agents to which it is related? Are we to consider them rickettsiae or viruses? Since at present there is not complete agreement among bacteriologists as to the precise definition of the genus rickettsiae and since the virus group is largely defined by negative characteristics and possibly contains agents of very different intrinsic nature which a natural biological classification would not place together, the matter becomes largely one of personal choice. Undoubtedly, those four agents resemble the rickettsiae in a number of points; they are minute in size and show pleomorphism, though not the bacillary and thread forms of typical rickettsiae; they do not stain easily with aniline dyes; they are Gram-negative; they stain easily with Giemsa and in their various morphological forms take a variety of tints from red to dark blue with this stain; they stain easily and specifically with Castañeda's stain; they are only little, if any, more filterable than rickettsiae; they are non-cultivable apart from living cells; they adopt an intracellular habitat. They differ from the majority of the rickettsiae in not possessing an arthropod host. In what respects do they differ from or resemble a typical large virus such as vaccinia? Up to the present, true initial bodies with basophil staining properties have not been described in a typical virus. Bland and Robinow[55] suggest that in vaccinia the smallest type of inclusion body is an analogue of the initial body, but its tinctorial quality is different. Lack of staining with aniline dyes and Gram-negativity are points in common with viruses as well as rickettsiae. The ease of staining of the four agents with Giemsa is not so much greater than that of vaccinia as to be relied on as a distinguishing character and the free elementary bodies of these agents take the same colour as vaccinia with this stain. Vaccinia does not stain with Castañeda's stain. Trachoma appears to be certainly less filterable than vaccinia but psittacosis is not greatly so. Non-cultivability and intracellular habitat are points which are shared both by viruses and rickettsiae. We may say then that these

four agents differ from the typical large virus: (1) In possessing initial bodies which stain blue with Giemsa and in showing greater pleomorphism; (2) In forming inclusions with a basophilic matrix; (3) In staining with Castañeda's stain. They differ from typical rickettsiae: (1) In lack of an arthropod host; (2) In not showing bacillary and thread forms; (3) In forming inclusions with a matrix. The four agents thus possess points of resemblance to both rickettsiae and viruses and some points in which they differ from both.

I myself consider that they stand in an intermediate position between the rickettsiae and the large viruses and may possibly form a biological link between them. For the present, I would prefer to group them with the viruses but to give them a distinctive position as the " basophilic viruses " on account of the blue staining of their initial bodies and of the matrix of their inclusions which distinguishes them from the larger typical viruses which do not possess blue initial bodies and whose inclusions are acidophilic.

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AN ANALYSIS OF ONE HUNDRED CASES OF STRABISMUS TREATED ORTHOPTICALLY*

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AN orthoptic department was started at the West Bromwich and District Hospital in March, 1941, not without some trepidation, as to whether the amount of work would justify the inception of such a department, and as to whether the work itself was really worth while. Fears regarding the amount of work were quickly dispelled by the rapid accumulation of a large waiting-list which

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increased by arithmetical progression with each succeeding month. Fears regarding the worth-whileness of the work were also speedily allayed. For the first time, one felt, squints were being given a square deal and not merely the sporting chance of recovery which might or might not follow the prescription of glasses, the patients as often as not being lost sight of until such time as parental solicitude or the patient's' *amour propre*, boiled up into a demand for the surgeon's art, to bring an errant eye back to the straight and narrow path from which it had deviated.

At the same time, the mere existence of a waiting-list of 100 patients, even coupled with a warm feeling of self-approbation at work well done, or at least well intended, were insufficient to set at rest the still small voice of scepticism which clamoured for appeasement, the more so since many of the pundits declared the whole thing to be vanity and vexation of spirit. It was, therefore, decided that the first 100 cases to pass through the complete course of treatment should be scrutinised, analysed and generally submitted to a ruthless evaluation of their binocular assets. This number was accomplished by November, 1943, and the scrutiny was conducted in February, 1944. The findings thereof form the basis of this article.

The main points upon which information was sought were :—

1. The deviation present at the conclusion of treatment compared with that present at the commencement, whether without or with recourse to operation.

2. The degree of binocular vision present at the conclusion of treatment compared with that existing at the commencement of treatment.

In other words it was sought to discover whether treatment produced :—

1. Orthopsis; 2. Stereopsis,

these being the two objectives which it seemed one was seeking to attain in the treatment of squints.

The material for review then, consisted of 100 consecutive cases, 51 females and 49 males, of ages from 5 to 12 years, the average being 9 years. The deviations present were from 3°-60°. Ninety-four were convergent and six were divergent. The average deviation was 19·45°. All were given orthoptic treatment, the duration of treatment being from 1 month to 16 months—the average being 4·67 months, treatments being given twice weekly.

Cases treated by orthoptic treatment only

Sixty-three cases were so treated.

(1) *Development of orthopsis* :—

23 of these became perfectly straight, the final deviation being 0°, the original deviations being from 3°-25°,—average 10°.

25 became almost straight, the final deviation being less than 5°, the original deviations being from 3°-20°,—average 10·35°.
15 did not become straight, the final deviation being over 5°, the original deviations being from 10°-30°,—average 16·8°.

These figures would appear to indicate that deviations of up to 25° may be successfully treated by orthoptic means alone, that success is more likely at the 10° level, but that not all cases of 10° or even less can be successfully treated.

The percentage of complete success in developing orthopsis in this group of 63 deviations of from 3°-30°, is 36·5 per cent.

(2) *Development of stereopsis* :—

36 cases developed good binocular and stereoscopic vision as tested by the synoptophore, cover testing, and Worth's lights. All of these commenced with simultaneous perception and fusion.
7 cases developed fair S.V., *5* commencing with S.P.F., *1* with S.P. and weak fusion, and *1* with no S.P.
20 cases developed no S.V., *1* commencing with S.P.F., *10* with no S.P., and *9* with abnormal retinal correspondence.

These figures would appear to indicate that the development of a good degree of S.V. is dependent upon having an original fair degree of binocular vision—S.P.F. or better—but that even some of those commencing with this degree may not develop good S.V.

Further analysis

Further analysis shows that,
of the 23 cases becoming straight, all commenced with S.P.F.
of the 25 cases becoming almost straight, 14 commenced with S.P.F., the remainder comprising 2 with S.P. and W.F., 3 with no S.P., and 5 with A.R.C.
of the 15 cases not becoming straight, 2 commenced with S.P.F., 9 with no S.P. and 4 with A.R.C.

It would appear therefore that the development of orthopsis by means of orthoptic treatment alone, depends to a large extent upon the degree of binocular vision obtaining at the commencement of treatment as well as on the degree of deviation; indeed that the possession of S.P.F. is an essential pre-requisite for success.

The possession of an original S.P.F. and the development of G.S.V. does not, however, mean that full orthopsis will necessarily be attained. Analysis of those 36 cases developing G.S.V. shows that 21 became straight and 15 near-straight, the average original deviation of the former being 15° and of the latter 10°.

Results of orthoptic treatment alone.—The findings are that,

of 100 cases, 36 became straight or near-straight and developed G.S.V. by means of orthoptic treatment alone, and it appeared that an essential condition of successful treatment was the pre-existence of S.P.F. and a squint of not more than 25°—preferably much less, viz., 10°.

Cases treated by orthoptic treatment plus operation

Thirty-seven cases were so treated.

(1) *Development of orthopsis* :—

6 of these became perfectly straight, the final deviation being 0°, the original deviations being from 20°-35°—average 29°.

17 became near-straight, the final deviation being 5° or less, the original deviations being from 15°-60°—average 33·1°.

14 cases did not become straight, the final deviations being over 5°, average original deviation 35·8°.

Results of Treatment by Orthoptic Treatment alone and of Orthoptic Treatment plus Operation.

	No. of cases	Straight	Straight and stereoscopic	Nearly straight	Nearly str. and stereo.	Not straight	Not stereo.
	—	23	—	25	—	15	—
Orthoptics only ...	63	—	—	—	—	—	—
	—	—	21	—	15	—	27
	—	6	—	17	—	14	—
Orthoptics plus op. ...	37	—	—	—	—	—	—
	—	—	4	—	5	—	28
	—	29	—	42	—	29	—
Total ...	100	—	—	—	—	—	—
	—	—	25	—	20	—	55

Of the 100 cases therefore :—

25 became perfectly straight and fully stereoscopic.

20 became almost straight and fully stereoscopic.

26 became straight or almost straight without becoming fully stereoscopic.

29 did not become either straight or stereoscopic.

(2) *Development of stereopsis* :—

10 cases developed G.S.V., 6 commencing with S.P.F. and 3 with no S.P.

7 cases developed F.S.V., 6 commencing with S.P.F. and 1 with no S.P.

3 cases developed P.S.V., 2 commencing with S.P.F. and 1 with no S.P.

17 cases developed no S.V., all commencing with no S.P. and 2 with A.R.C.

Further analysis shows that of the 10 cases developing G.S.V., all became straight or near-straight except one; of the 7 cases developing F.S.V., 5 became straight or near-straight; and that of the remaining 20 developing poor or no S.V., 8 only became straight or near-straight.

That is, the majority of those having G.S.V. became straight and remained straight, and the majority of those not having S.V. did not become straight; which would seem to indicate that the development of S.V. is an important factor in maintaining straightness of the eyes following operation.

Controls

In order to meet the criticism that perhaps some of the cases might have become straight without treatment, it was thought desirable to check the results of treatment against a series of comparable cases which had no treatment except the wearing of glasses. Cases on the waiting-list provided a ready means of doing this. A consecutive series of 50 cases was chosen, all of which had been on the waiting-list for over 5 months, some longer—up to 26 months—the average being 9·2 months; 33 were males, 17 were females, their ages being from 4-13—average 6·2 years. The angles of deviation were from 5°-55°—average 22·40°. In not a single case had the squint become reduced to nil, *i.e.*, there was no case of spontaneous cure.

In eleven cases, there was a reduction of the squint, the average commencing squint being 24°, and the average resulting squint being 17°—average reduction 6·7°.

The remainder were either stationary or had got worse.

Nine cases had S.P.F. and 4 had weak S.P. to commence with. The remainder had no S.P. or worse. It goes without saying that no further degree of binocular vision was developed during the waiting period, but this was confirmed in all cases by the usual tests.

A comparison of the group treated by orthoptic treatment, with the group treated by glasses alone shows an incomparable superiority of results in the former group as against the latter, *viz.*, 36·5 per cent. cures as against 0 per cent.

Nature of refractive errors found and results of wearing glasses in the series of 100

Of the 100 cases treated by orthoptic means, 87 were hypermetropic in one or both eyes, the errors being from 0·25D. to 6·0D.—average 2·75D. In 44 of these there was an astigmatism of over 0·50D., the majority being from 1-2D.

Twelve cases were emmetropic.

One was myopic, with a divergent strabismus.

There did not appear to be any relationship between the degree of squint and the degree of error present. Thus the highest error of 6D. and 5D. had a deviation of 5° and the highest deviation of 60° had an error of 0·50D. and 1·0D. Nor was divergent strabismus found to be necessarily associated with myopia, since of the 6 divergers, one was myopic—3 were emmetropic and 2 were hypermetropic of low degree.

The results of correction by glasses were as follows :—

3 cases only were straight with glasses at the commencement of treatment by orthoptics, the original deviations being from 5°-15°—average 10°; all three commenced with S.P.F. and developed G.S.V.

25 cases showed a reduction of squint, the average commencing squint being 18·4° (5° to 50°), and the average squint with glasses being 8·1° (5° to 20°), the average reduction in squint being 11°. Twenty of these commenced with S.P.F. and 18 developed G.S.V.

44 cases showed no alteration in the degree of squint, the average degree in this series being 21·7° (3° to 60°); 14 of those commenced with S.P.F. and 13 developed G.S.V.

Of those cases becoming straight with glasses, therefore *100* per cent. commenced with S.P.F. and developed G.S.V.

Of those cases showing a reduction with glasses, *80* per cent. commenced with S.P.F. and 72 per cent. developed G.S.V.

Of those cases showing no reduction with glasses, *31* per cent. commenced with S.P.F. and 27 per cent. developed G.S.V.

These figures would appear to show that the cases developing orthopsis as a result of wearing glasses only, are those with the lower degrees of squint, *viz.*, 5° to 15°, but that the possession of S.P.F. and a capacity for the development of G.S.V. is an essential condition of this eventuality.

Of the 44 cases showing no reduction with glasses, however, 13 were of 10° or less, and 5 of these commenced with S.P.F. and developed G.S.V. with treatment, so that not all such cases become straight with glasses. As a result of orthoptic treatment,

however, all 5 became sraight, which would seem to indicate the value of orthoptics over the simple wearing of glasses.

Conclusions

A survey of this kind naturally leads one to consider whether it sheds any light on the causation of concomitant strabismus in childhood. Is it due to a defect in the neuro-muscular mechanism, whereby orthopsis cannot be maintained, the capacity for binocular vision being unaffected, or is it a failure of the capacity for binocular vision, the neuro-muscular mechanism being intact, but having no stimulus to maintain orthopsis?

Regarding the first possibility, the existence of hypermetropia with consequent over-accommodation, associated with over-convergence has been adduced as an explanation of the development of internal strabismus, but as against this, hypermetropia is a normal condition in childhood, 60 per cent. of children at 10 years of age being hypermetropic (Parsons); there is an ample reserve of accommodation to compensate for it, *viz.*, 14D. at 10 years (Parsons). All cases of internal strabismus are not hypermetropic, and the degree of strabismus appears to bear no relationship to the degree of hypermetropia. Correction of the hypermetropia does not appear to correct the squint in the majority of cases. Also one frequently encounters cases of high hypermetropia—10D. and over—in which there is no history of strabismus. It would appear, therefore, that although hypermetropia may be a factor in determining an inward deviation of the eye rather than an outward one, it is not the main aetiological factor.

There is no question of failure of movement. Eye movements are full in all directions. There is no failure of comitancy. There is, however, a failure in the orientation of the eyes with regard to each other. This might conceivably be due to some failure in the neuro-muscular mechanism, in which case, if the strabismus is corrected by operation, the eyes should remain straight, but it would appear that in the absence of good binocular vision, the tendency is for them not to do so.

Regarding the second possibility; the absence of stereoscopic vision is the one factor common to all cases. Those cases having the greatest capacity for education or re-education in respect of stereoscopic vision, are the ones having the best prognosis as regards cure. Thus those cases having S.P.F. to commence with and developing G.S.V., form the majority of cases becoming straight and remaining straight, whether treated by means of glasses only, or by means of orthoptic treatment plus glasses, or by orthoptic treatment plus glasses plus operation. It would,

therefore appear that the absence of or failure of S.V. is the chief factor in the causation of concomitant strabismus.

Objections to this theory spring to mind at once: What about the strange phenomenon of abnormal retinal correspondence the existence of which would appear to indicate that the brain is determined to see binocularly in spite of uniocular recalcitrancy. Binocular vision is not stereoscopic vision, however, and no such cases seem capable of developing stereoscopic vision. Suppression would seem to be more easily achieved for macular vision than for peripheral vision and macular vision is essential for stereoscopic vision (*vide Brit. Jl. Opth.*, October, 1938). Another objection is that if failure of stereoscopic vision is the cause of the strabismus, then re-establishment of stereoscopic vision should correct the strabismus in all cases. It does not, however, necessarily follow that this must be so, since with the establishment of a squint, new factors may be initiated, which have nothing to do with the original cause. A disorientation of the eyes has taken place, which is not necessarily amenable to correction, even by the establishment of stereoscopic vision, and may require an operation to produce correction, but this would not invalidate the primacy of stereoscopic failure in the causation of the condition. Following upon operation, it is those cases having good stereoscopic vision which are most likely to remain straight.

Summary

The genesis of the survey is described, namely a desire to ascertain at first hand the effects of orthoptic treatment in developing: 1, Orthopsis; 2, Stereopsis.

2. An analysis is made of 63 cases treated by orthoptic means only, the findings being that 36 became straight or nearly straight and developed good stereoscopic vision. The conclusion is reached that an essential pre-requisite to successful treatment by orthoptics only, is the existence of S.P.F. and a strabismus of not more than 25°, preferably much less, *viz.*, about 10°.

3. An analysis is made of 37 cases treated by orthoptic treatment plus operation, the findings being that 23 became straight or nearly straight, and 17 developed good or fair stereoscopic vision, and the conclusion is reached that G.S.V. is an important factor in maintaining orthopsis even where operation has been performed.

4. Analysis is made of a control series of 50 cases which were under observation for an average of 9 months, and had no treatment except the prescription of glasses. The findings are that none of these developed orthopsis or stereoscopic vision.

5. An analysis is made of the refractive findings in the 100

cases under review, and of the effects present as a result of wearing glasses at the commencement of treatment by orthopsis. The findings are that 3 only were straight with glasses, 25 showed reduction, and 44 showed no change, and the conclusion is reached that the lower degrees of squint are most likely to become straight with glasses, but then an essential condition of this eventuality is the pre-existence of S.P.F. and a capacity for developing G.S.V.: that not even all such became straight, but that with the addition or orthoptic treatment they are very likely to do so.

6. The possible causation of strabismus in the light of these findings is discussed, and the conclusion is reached that the absence of or failure of S.V. is the main aetiological factor in the production of concomitant strabismus.

7. Some objections to this theory are discussed, but are not thought to invalidate it.

My best thanks are due to Miss M. Levinge, Orthoptist at the West Bromwich and District Hospital, without whose willing and enthusiastic help this investigation would have been impossible.

Abbreviations

S.V. = Stereoscopic Vision.
G.S.V. = Good Stereoscopic Vision.
F.S.V. = Fair Stereoscopic Vision.
P.S.V. = Poor Stereoscopic Vision.
S.P. = Simultaneous Perception.
S.P.F. = Simultaneous Perception and Fusion.
W.F. = Weak Fusion.
A.R.C. = Abnormal Retinal Correspondence.

PENETRATION OF PENICILLIN INTO THE EYE*

BY

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and

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A FEW observations have been made on the penetration of penicillin into the eye after administration in various ways. Aqueous humour was collected by one of us (R.E.W.) and examined in the laboratory (C.H.S.-H.) by techniques designed to reveal the presence of substances inhibitory to bacteria. Table I shows clinical details, mode of administration of penicillin and interval between therapy and collection of aqueous humour.

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Clinical technique

The continuous irrigation or drip into the conjunctival sac was carried out as suggested by one of us (R.E.W., 1944).

Before performing paracentesis of the anterior chamber four instillations of 4 per cent. cocaine hydrochloride were given. The usual precautions to attain sterility of apparatus and avoid introducing intra-ocular infection were taken. The conjunctival sac was irrigated with sterile normal saline for 2 minutes prior to penetrating the cornea. The syringe used for withdrawing aqueous humour was an all-glass tuberculin syringe, the needle of fine calibre with short bevelled point. Since this type of needle does not penetrate the cornea without undesirable pressure trauma, it was introduced along the track of a preliminary puncture with a Bowman's needle. The syringe containing aqueous fluid was passed immediately to the laboratory. Permission was obtained for paracentesis when this was not indicated as a therapeutic procedure. Penicillin administration by corneal bath was not investigated as suitable contact apparatus was not available. Captain H. Duncan, R.C.A.M.C., kindly gave a verbal description of the technique of penicillin iontophoresis as used by Dr. MacMillan, Professor of Ophthalmology, Royal Victoria Hospital, Montreal, in the Physiotherapy Department of that institution, and on this an improvised technique was based. We have to thank him also for giving us access to the two battle casualties referred to in the series of cases which were under his care at No. 4 Canadian General Hospital. The galvanic apparatus used for intranasal iontophoresis at the Military Hospital was employed. The current tension was 40 volts. The indifferent electrode (zinc sheet suitably padded with moist absorbent and insulated from the table) was placed behind the patient's neck or shoulders and connected with the positive pole of the battery. Precautions for insulating the apparatus were taken. Since an active electrode especially constructed for the purpose was not available an improvised electrode was tentatively employed. We understand that an electrode similar to that in the Royal Victoria Hospital was made subsequently by Messrs. John Weiss for Lt.-Col. Elkington, Consulting Ophthalmic Surgeon, R.C.A.M.C. In Case 10 our active electrode consisted of a rubber vaccine-bottle cap filled with absorbent cotton which projected from the open end. This was saturated with penicillin solution (sodium salt) 1000 u/c.c. dissolved in normal saline. A sharp needle terminal connected with the negative pole perforated the convexity of the cap and made contact with the absorbent cotton. The projecting saturated cotton covered the whole corneal surface. Fresh solution was run in to the projecting cotton from time to time during the passage of the

current. No speculum was used. A current of 2 mm. amps. was let in gradually and passed for 5 minutes. This crude electrode although unsatisfactory seemed to answer the purpose without any undesirable complications. Cocaine hydrochloride 4 per cent. drops were used for surface anaesthesia.

In case 12 a metal speculum was used and a pack of absorbent cotton saturated with the penicillin solution was built up on the cornea. The apex of the cotton was contacted with the negative needle terminal. The penicillin solution saturating the cotton was replenished with a pipette during the passage of the current. This was not satisfactory and a corneal nebula was produced. It was obvious that a carefully constructed active electrode was essential for iontophoresis therapy, but our improvised technique served to establish the fact of the penetration of penicillin ions to the aqueous humour through the undamaged or partially damaged cornea. In case 11 (b) a similar procedure was adopted without damage to the cornea.

Bacteriological technique

The first six specimens were examined for penicillin by the technique of inhibition of colony formation by the Oxford "H" strain of staphylococcus aureus in slide-cells (Bigger, et al, 1944). The aqueous humour or serum was diluted in volumes of a normal human serum, 0·25 c.c. of each dilution were inoculated with a standard loopful of a 1/1000 dilution of an 18-hour broth culture of the staphylococcus, and with each dilution a slide-cell was filled. The cells were incubated for 20 hours. Counts were then made of the number of visible colonies and the results were compared with the colony counts in normal serum and in serum in which dilutions of a "standard" penicillin solution had been made. This "standard" was prepared by dilution of therapeutic penicillin and was assayed by the Heatley plate technique (Heatley, 1944). Because of the need to dilute the aqueous humour at least once with serum in order to support the growth of staphylococcal colonies, the highest concentration of aqueous humour examined in this way was a 1 : 2 dilution.

The remaining specimens were examined both by the above technique and by the technique of Fleming (1945). In the latter case, dilutions of aqueous humour in saline, to which 50 per cent. defibrinated human group "O" blood, infected with an 18-hour culture of a haemolytic streptococcus was added, were incubated in capillary tubes in the horizontal position. After 18 hours incubation, the tubes were stood in the vertical position and the degree of haemolysis of the red cells estimated as an indication of bacterial growth. Dilutions of a "standard" penicillin solution

and normal serum were used as controls. Because of the nutrient property of the added blood, neat aqueous humour could be examined. The method was slightly more sensitive than the slide-cell technique but the estimated content of penicillin in terms of the "standard" was the same in the aqueous humours or sera examined by both methods.

Results

Fifteen specimens of aqueous humour and three of serum were examined from eleven patients. Table II sets out the results of the various estimations on the various specimens of aqueous humour. Positive bacteriostasis (column 4) was defined by the absence of colony formation at some dilution or other in the slide-cell test, or by complete absence of haemolysis in the streptococcal test. The figures in column 5 give the highest dilution of fluid with entire absence of colonies in the appropriate slide-cell except in the case of the specimens marked with an asterisk. These two fluids had no bacteriostatic effect when diluted and examined by slide-cell test but undiluted fluid in each case completely prevented haemolysis in the streptococcal test. The estimated penicillin content (column 6) was calculated by comparison of the results with the penicillin "standard" solution examined at the same time and by the same technique.

The table shows that fluids from cases 1, 7, 10, 11 and 12 had detectable inhibitory action. The estimated concentration of penicillin was 1/16 Oxford unit per c.c., $\frac{1}{8}$ unit and $\frac{1}{4}$ unit respectively in three instances, one unit in three instances and two units in the seventh specimen. The results showed that penicillin either does not pass into the aqueous humour from the blood or reaches a much lower concentration than that present in the serum. The level of penicillin in serum collected at the same time as the collection of aqueous humour was estimated in cases 8 and 11. The serum from case 8 had an estimated 4 units of penicillin per c.c., that from case 11 collected 30 minutes after the intra-muscular penicillin had 4 units per c.c., and 60 minutes after the injection of penicillin there was still 2 units per c.c. in the serum. The aqueous humour from case 8 was devoid of penicillin, that from case 11 (a), 30 minutes after the penicillin showed inhibition in neat fluid (1/16 unit of penicillin) and at 60 minutes no inhibition was detected in the secondary aqueous humour at 1 : 2 but the fluid was not examined undiluted. On another occasion (11(b)), secondary aqueous collected 80 minutes after intra-muscular penicillin gave complete bacteriostasis at a dilution of 1 : 2 but higher dilutions were not tested. The fluid from all three eyes treated by ionisation, showed strongly inhibitory action (1 unit per c.c.), but

TABLE I

Case No.	Condition of Eye	Local Treatment (if any) prior to Investigation	Method of Penicillin Administration	Interval between Administration and collection of Aqueous Humour or Blood	Remarks
2	Battle trauma flying fragment. Globe not ruptured. Lens cataractous. Anterior capsule torn. Flakes of lens matter in aqueous humour	Gutt. Atropinae	No Penicillin used	—	No blood in anterior chamber. 0·15 c.c. clear aqueous humour collected before evacuation of lens matter
3	Normal	—	No Penicillin used	—	0·20 c.c. clear aqueous humour collected
4	Recurring Keratitis of H. febrilis type corneal involvement slight. Process not now active	Gutt. Atropinae	Gutt. Penicillin solution sodium salt 1000 u/c.c. every 2 hours. 10 instillations	3 hours	0·20 c.c. clear aqueous humour collected
9	Dendritic ulcer not extensive, healing but still staining	Gutt. Atropinae	Penicillin lamellae (Ca. salt), each 25 o.u. One every hour for six hours	½ hour	0·20 c.c. clear aqueous humour collected
1	Residual deep Keratitis following Herpes Ophth. Extensive corneal haze, swollen epithelium, diffuse faint staining of whole surface	Gutt. Atropinae	Solution Penicillin (sodium salt) 1000 u/c.c. *continuous* drip irrigation of conjunctival sac. Approx. 2 drops per minute for 20 hours	3 hours	0·20 c.c. clear aqueous humour collected but aqueous humour clotted in syringe, presumably plasmoid
6	Normal	—	ditto	3 hours	0·20 c.c. clear aqueous humour collected. Drip failed to function during night. Uncertain how many hours cornea conjunctiva bathed by solution
7	Normal	—	ditto	3 hours	0·25 c.c. clear aqueous humour collected

TABLE I—*continued*

Case		Local Treatment		Interval between Admin-	

TABLE I—*continued*

Case No.	Condition of Eye	Local Treatment (if any) prior to Investigation	Method of Penicillin Administration	Interval between Administration and Collection of Aqueous Humour or Blood	Remarks
5	Battle casualty—multiple body injuries. Eye struck by non-penetrating missile, severe impact, traumatic cataract, lens capsule intact. Iridodialysis, no blood in anterior chamber	Gutt. Atropinae	I. Muscular injection 15,000 o./u. every 3 hours for 5 days	3½ hours	0·20 c.c. clear aqueous humour collected. Did not clot
8	Normal	—	I. Mus. injection 85,000 o./u. single dose	35 minutes	0·20 c.c. clear aqueous humour collected
11 (a)	Kerato conjunctivitis, limbal lesions	Gutt. Atropinae	I. Mus. injection 100,000 o./u.	Primary Aq. hum. 30 minutes Secondary Aq hum. 60 minutes	0·20 c.c. clear aqueous humour collected 0·20 c.c. clear aqueous humour collected
11 (b)	Normal	—	I. Mus. injection 100,000 o./u.	Primary Aq. hum. 40 minutes Secondary Aq. hum. 80 minutes	0·10 c.c. clear aqueous humour collected 0·20 c c. clear aqueous humour collected (Primary aq. hum. not listed owing to failure of strep. culture to grow)
10 (a)	R. E. Normal	—	Iontophoresis penicillin (sodium salt) 1000 u/c.c. 2 milliamps for 5 minutes	½ hour	Application gave no discomfort. 0·20 c.c. aq. humour collected. 4 instillations of 4 per cent. Cocaine hydrochlor.
10 (b)	L. E. Keratitis disciformis of some 4 weeks standing	Gutt. Atropinae	Iontophoresis penicillin (sodium salt) 1000 u/c.c. 2 milliamps for 5 minutes	½ hour	Application slightly painful (in spite of 4 instillations of 4 per cent. Cocaine hydrochlor). 0·20 c.c. Aq. hum. collected
12	Kerato conjunctivitis, limbal foci in inferior temporal quadrant of some standing. Eye relatively quiet	Gutt. Atropinae	Iontophoresis penicillin (sodium salt) 1000 u/c.c. 2 milliamps for 5 minutes	½ hour	Patient complained of slight pain. At end of application central round pearly-grey haze of cornea about 4 mm. diameter observed. In 3 weeks nebula much smaller. Exact time of clearing uncertain, cornea clear in 4 months. Cocaine guttae as above

TABLE II

Case No.	Treatment	Highest concentration of aqueous humour examined	Presence of Bacteriostasis	Highest dilution of fluid with Bacteriostasis	Estimated Penicillin content of Aqueous Humour
2	None	1 : 2	O	—	—
3		1 : 2	O	—	—
4	Penicillin guttae	1 : 2	O	—	—
9	Penicillin lamellae	1 : 2	O	—	—
1	Penicillin irrigation	1 : 2	+	1 : 16	2 units
3		1 : 4	O	—	—
7		1 : 1	+	1 : 1*	1/8 unit
5	Penicillin intramuscularly	1 : 2	O	—	—
8		1 : 1	O	—	—
11 (a)	Primary aqueous	1 : 1	+	1 : 1*	1/16 unit
	Secondary aqueous	1 . 2	O	—	—
11 (b)	Secondary aqueous	1 : 2	+	1 : 2	1/4 unit
10 (a)	Penicillin ionisation	1 : 4	+	1 : 8	1 unit
10 (b)		1 : 4	+	1 : 8	1 unit
12		1 : 2	+	1 : 8	1 unit

* Aqueous examined only by Fleming technique.

in only one of the three eyes treated with irrigation of penicillin solution was a comparable inhibition obtained (2 units per c.c.). The other two eyes irrigated with a comparable strength of penicillin and for a like period showed an absence of inhibition in humour diluted 1 : 4. Undiluted fluid from one of the latter cases gave inhibition of streptococcal haemolysis and had an estimated content of penicillin of $\frac{1}{8}$ unit.

Discussion

It is emphasised that these observations are incomplete because work was interrupted by circumstances beyond our control.* We felt, however, that observations on the human aqueous humour were sufficiently interesting to record, particularly as they tended to support the results of Von Sallmann and Meyer (1944) obtained with animals. Our results showed that penicillin was capable of traversing the human cornea when introduced into the conjunctival

* The work ended December, 1944.

sac by continuous irrigation with a solution. The damaged cornea of one of our patients (case 1) apparently allowed considerable penetration but the normal cornea (case 7) was less permeable. A damaged epithelium (especially if oedematous throughout as in case 1), or a cocainised epithelium probably behave as would epithelium treated with a wetting solution. When penicillin was administered intramuscularly, it appeared in the aqueous humour of both primary and secondary types but in very much lower concentration than that attained in the serum. Higher intra-ocular concentrations than those found after intramuscular penicillin were produced in each eye subjected to iontophoresis, but the improvised apparatus employed by us produced an undesirable complication (corneal nebula). It is, at present, impossible to define the concentration of penicillin in either blood or tissue fluid necessary for therapeutic effect. It may be, that the small amounts of penicillin reaching the aqueous humour after intramuscular penicillin or penicillin baths, will prove to be clinically adequate. The fact that high intra-ocular concentrations can be obtained by the iontophoresis method is, however, in our view significant and probably worthy of further investigation.

Summary

Observations designed to indicate the most effective method of introducing penicillin into the eye are recorded. Penicillin reaches the aqueous humour after local use in the conjunctival sac or after intramuscular injection but the concentrations attained are variable and often low. By the use of iontophoresis, higher intra-ocular concentration can be obtained but the technique requires considerable care and attention.

Note on the technique of ioptophoresis

With regard to the general detail of iontophoresis technique and the various theoretical factors governing its use, reference should be made to Karbowski's paper on this subject. It is essential to employ the correct type of iontophoresis apparatus and pay careful attention to the detail of technique in order to avoid complications. The design of the active electrode is most important. Various patterns described in the literature would no doubt serve for penicillin but here we need only refer to one which has been used without complications by Dr. MacMillan in the Physiotherapy Department of the Royal Victoria Hospital, Montreal, the detail of which has been given to us through the courtesy of Captain Duncan and Miss Rose of that Department. It consists of a zinc rod about $2\frac{1}{2}$ inches long with an expanded base $\frac{1}{4}$ inch or more in diameter. This fits into a slightly tapered glass tube about $2\frac{3}{4}$ inches long with a lateral opening near its middle and a smooth

mouth somewhat greater in diameter than the average cornea. The top of the zinc rod and the narrower end of the glass tube are engaged and held by a metal handle about 2 inches long which can be coupled to the negative pole of the battery. The zinc rod is held in the glass tube in such a way that its expanded foot is about 1 inch from its wider open end. This end of the tube is packed with absorbent cotton, which contacts the zinc above and projects slightly from the mouth of the tube. The cotton is saturated with penicillin solution 500 u/c.c. (in normal saline), and recharged during treatment with fresh solution from a syringe through the lateral opening. With this electrode a current of 2 milliamps is passed for 3 minutes the first day, and thereafter daily for 9 days 2 milliamps for 5 minutes. No speculum is used, the current is let in gradually being controlled (presumably) by transformer and resistance. Pantocaine ½ per cent. is used in preference to cocaine. Provided suitable apparatus and technique are used penicillin may be introduced into the globe (undamaged or unruptured) repeatedly via the cornea by iontophoresis. The method has obvious advantages over the repeated introduction of penicillin by means of a needle and syringe in such cases. To effect penetration to the vitreous, applications longer than 5 minutes are likely to be required, but increase in the time of application increases the risk of corneal damage. Only further experience can determine the maximum time of application at each treatment.

We wish to thank Major General L. T. Poole, C.B., D.S.O., Director of Pathology War Office and Brigadier Sir Stewart Duke-Elder, Consulting Ophthalmic Surgeon to the Army for providing facilities for this work to be carried out and for permitting its publication.

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ANNOTATION

The danger of spot diagnosis

The importance of never saying anything to a patient, either in the consulting room, out-patient department, or at the bedside, which can even indirectly lead the hearer to infer a very bad prognosis is obvious, but not always sufficiently remembered. People

have been known to commit suicide after hearing what has practically amounted to a death sentence, and similar disastrous results have followed an unguarded remark about imminent blindness. Patients also, it is worth while remembering, often half hear, only half understand, and put a totally wrong construction on what has been said to them; so it behoves one to be careful.

Such a thing happened a good many years ago in relation to a middle-aged female who had been admitted to hospital with double choked discs. It is true that no tragic result occurred to the patient. The tragedy was the other way. As a preliminary she was referred to a neurologist. He entered the ward accompanied by a class of students, and noticing something odd about the facial appearance of the patient, immediately made a mental diagnosis of middle fossa tumour, told his class that such a condition was always due to secondary malignant deposits and searched for a primary focus. Having found a small hard lump in one of the breasts, he went on to demonstrate the case to his class and gave a very gloomy prognosis. The patient was exceedingly angry and immediately took her discharge. She went to another hospital, and there someone remembered his first lines and had the Wassermann reaction done. It was strongly positive, and a course of anti-syphilitic treatment cured the ocular condition. To make certain, however, a surgeon was called in; he removed the lump in the breast, which turned out to be innocent.

There is an irresistable urge, when taking a class of students, to make lightning diagnoses. Mostly these succeed, but at times, as in this instance, the maker is let down badly. It is not given to all of us to be so handy with the ophthalmoscope as the apocryphal pan-diagnostician, who was said to have diagnosed an ovarian cyst from a moment's observation of the fundus; and better results will be obtained if we keep an open mind and stick to the known facts. So if any of our readers are smitten with a craving for spot diagnosis, let them remember the Horatian maxim *Festina Lente.*

ABSTRACTS

MEDICAL OPHTHALMOLOGY

(1) **Burch, F. E. (St. Paul, Minnesota).—Metastatic orbital infection.** *Amer. Jl. Ophthal.*, Vol. XXVI, p. 253, 1943.

(1) **Burch** reviews some of the literature on metastatic orbital infection. He describes the case of a white man, aged 39 years, who developed a left orbital abscess 24 days after a furuncle within

the left ala nasi and basal pulmonary infiltration due to type V pneumococcus. Haemolytic staphylococcus aureus was recovered from both lungs, the furuncle and the blood.

Large doses of sulphathiazole, 32 gm. daily, produced clinical improvement, but the white cell count fell from 32,200 per c.mm. to to 1,900 per c.mm.

The left orbital abscess was diagnosed by the insertion of a aspiration needle, and was drained through the lower lid and at a later recurrence through the upper lid. Ipsilateral papilloedema was evident during the illness. After eight and a half months, proptosis was only 1 mm., and vision had recovered to 20/15. Some diplopia persisted in the extreme right upper field.

H. B. STALLARD.

(2) **Atkinson, W. S. (Waterton, New York).—A coloured reflex from the anterior capsule of the lens which occurs in mercurialism.** *Amer. Jl. Ophthal.*, Vol. XXVI, p. 685, 1943.

(2) **Atkinson** describes a brownish coloured reflex from the anterior capsule of the lens which occurs in cases of chronic mercurialism. This reflex is also found in those who have worked a long time in mercury although they may exhibit no symptoms of mercurialism. The colour of the reflex is deeper in the pupillary area and it varies in different individuals from a light brownish grey to a deep rose brown. Small, round, punched-out defects and cracks often appear in the reflex. These resemble the behaviour of metallic mercury. Glass lenses exposed to mercury vapour present a similar brown reflex. The reflex may appear before signs of mercurialism are present.

H. B. STALLARD.

(3) **Baer, A. T. (Kansas City, Missouri).—The vitamins in ophthalmology.** *Amer. Jl. Ophthal.*, Vol. XXVI, p. 286, 1943.

(3) **Baer** comments that the modern trend is away from prescribing vitamins in a single pure form and there is a return to including the whole group or complex. The vitamin A requirement is 5,600 I.U. a day, but in disease much higher amounts may be needed. The addition of minute doses of a compound iodine solution greatly adds to the efficiency of vitamin A. The body requirement of vitamin B_1 is a minimum of 300 I.U. or 1 mg. per day for the prevention of beri-beri. The amount of thiamin chloride eliminated by the kidneys is used as an index in the diagnosis of vitamin B_1 deficiency. The parts played by vitamins C, D and K in the maintenance of ocular health and in certain pathological states of the cornea and lens, in particular, are discussed.

H. B. STALLARD.

(4) **Harley, R. D. (Ancon, Canal Zone).—Ocular myiasis (ophthalmomyiasis).** *Amer. Jl. Ophthal.*, Vol. XXVI, p. 742, 1943.

(4) **Harley's** case illustrates how the larval form of a botfly masqueraded as a chalazion. There appeared a pinpoint opening in the skin over the swelling in the upper lid and through this passed minute bubbles. The swelling was incised and there was removed a white flask-shaped mass 15 mm. in length which gave evidence of life. Larva of the human botfly, dermatobia hominis, were identified. Removal is facilitated by anaesthetising or killing the pest by mercury bichloride soaks, for it is covered with many tiny bristles which in life make difficult its extraction from the tissues.

H. B. STALLARD.

BOOK NOTICE

Cataract and Anomalies of the Lens. By JOHN G. BELLOWS, M.D., PH.D. London: Henry Kimpton. 1944.

This book is a most valuable addition to ophthalmology, and the author is to be congratulated on the clarity of the text and the excellence of the diagrams and illustrations.

Clinicians and research students alike will find a comprehensive account of both rare and ordinary conditions of the lens, and their interest cannot fail to be stimulated by the continuity and brilliance of the subject matter.

In his account of the metabolism and chemical composition of the lens, as well as the pathogenesis of cataract, it is evident that the author has spent an immense amount of time in surveying the evidence of scientific work. He has set into order a host of recorded facts, and has not only made this subject more intelligible to the ophthalmic surgeon, but has provided a basis of reference for the research student. Wherever possible he has correlated the chemistry of the lens with that of the body as a whole.

The structure and development of the normal lens are well described, as well as the various forms of cataract. There is, in addition, a good account of certain rare forms of cataract, *e.g.*, those due to radiant energy, electricity and toxins, concerning which it was previously difficult to obtain information. Finally, there is an adequate description of operative procedures, together with the complications which may follow them.

OBITUARY

N. BISHOP HARMAN

NATHANIEL BISHOP HARMAN, whose death was briefly announced in our pages last month, was born in London in 1869. Educated at the City of London School, he was a scholar of St. John's College, Cambridge, and graduated with a double first in the Natural Sciences Tripos in 1897. Coming to London he joined the medical school of the Middlesex Hospital, where he came under the influence of William Lang, with whom he worked in the Eye Department for many years as clinical assistant. He took the M.B., B.Ch.Cantab. and the F.R.C.S.Eng. in 1898 and did a great deal of anatomical teaching both at Cambridge and in London, before he went out to South Africa as a Civil Surgeon in the Boer War. For his service he had the Queen's medal with five clasps. At Moorfields he worked with Treacher Collins, who in the early years of the present century had a remarkable band of chief clinical assistants, among them, Hancock, Mayou and Bishop Harman.

He was elected ophthalmic surgeon to the Belgrave Hospital for Children and later to the West London Hospital, where he was also lecturer in ophthalmology at the post-graduate medical school.

Ophthalmologically speaking, he will be best remembered for the work which he did with the late James Kerr in the foundation of special classes in the schools of the L.C.C. education authority, where partially sighted children were segregated and taught by special methods. Later these classes were centralized at various schools for the defective sighted which were called myope schools. In this work he was truly a pioneer, and it has had a lasting influence on the prevention of blindness, a subject in which he was always keenly interested. Harman served as consulting ophthalmologist to the L.C.C., and later played a leading part in setting up the National Eye Service. Much of his spare time was spent in furthering the work of the B.M.A. For ten years he was Treasurer of the Association, he received its gold medal in 1931, and quite recently was honoured by being elected a vice-president. During the 1914-18 War he was joint secretary of the Central Medical War Committee. And he was a Direct Representative on the General Medical Council for a period of years.

Harman joined the Ophthalmological Society of the United Kingdom 45 years ago and contributed many papers to its Transactions. He was a prolific author, and his "Aids to Ophthalmology" reached its eighth edition. It is one of the best of the "Aids" series, and has been the mainstay of the knowledge of eye diseases of many a medical student. His diaphragm test for binocular vision was demonstrated at the Ophthalmological Society in 1909, and immediately became a most popular instrument, of great help in

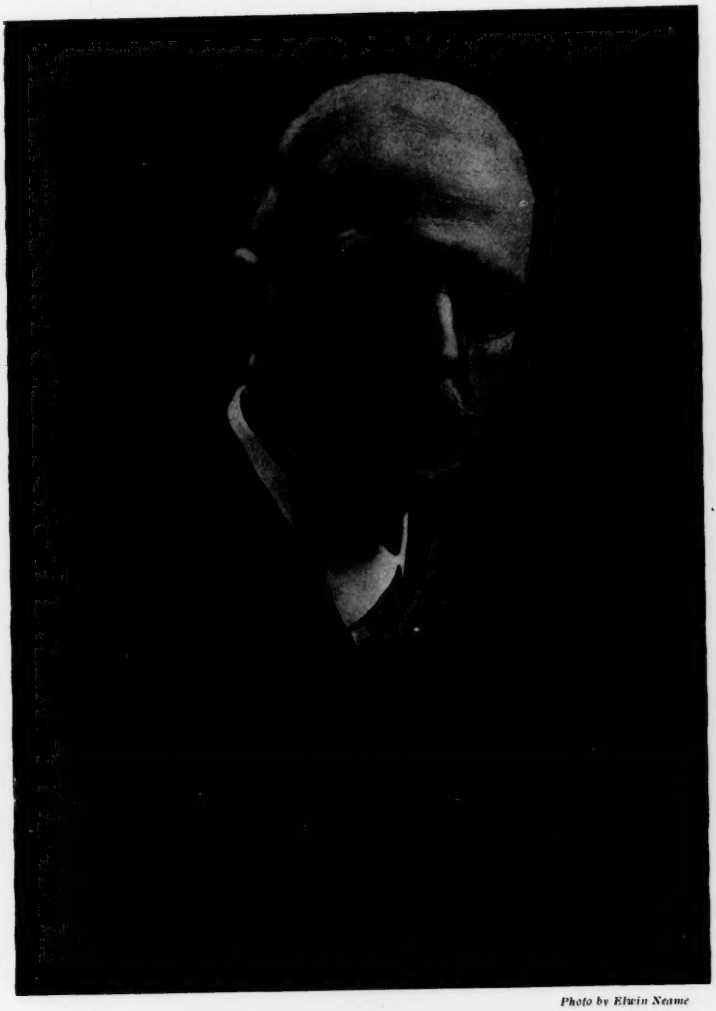
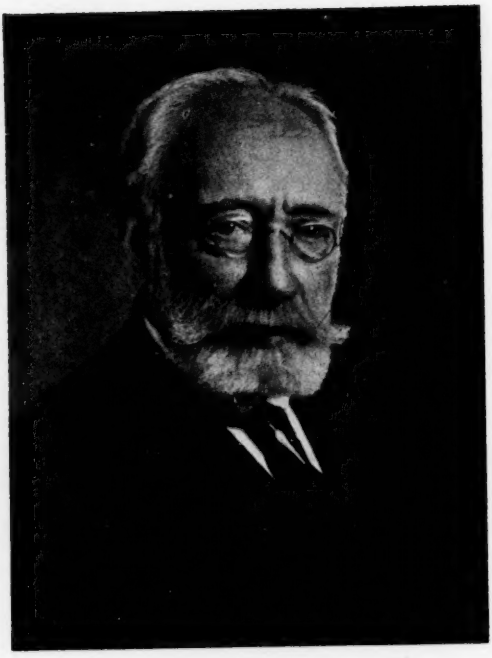


Photo by Elwin Neame

N. BISHOP HARMAN
1869-1945



Goram Norrie.

detecting malingerers. He was gifted with marked manual dexterity, and several useful modifications of ophthalmic instruments are due to him.

With his flaxen hair and tall stature he presented a distinguished appearance. At times militant, as the writer remembers him at a meeting of the members of the honorary staffs of the London Hospitals, with Sir Rickman Godlee in the chair, before the passing of the National Insurance Act; and as he got older, looking more benevolent, he was always worth listening to. Whether he was demonstrating his diaphragm test, or in lighter moods, when showing a pair of green glasses which had come from Delhi during the Mutiny, he commanded attention and respect.

He had a singularly alert brain, and was a good speaker with a ready sense of humour. British ophthalmology owes him a deep debt of gratitude, and much of his work will stand the test of time and not be forgotten. To his widow, herself a qualified doctor, and his four children we offer the sincere sympathy of British ophthalmology in their bereavement.

DR. GORDON NORRIE

NEWS of the death of Dr. Gordon Norrie of Copenhagen on October 11, 1941, has just reached us. He was fortunate in that he died after a very short illness, and before the worst horrors of the German occupation of Denmark had begun.

Of Scottish ancestry, Dr. Norrie was born May 6, 1855, in Elsinore, the son of William Gordon Norrie and his wife, Fanny Wright. He was educated in Copenhagen, practised speaking English with his grandfather, who had gone from Scotland to settle as a merchant in Denmark, and entered the University of Copenhagen in 1873. He qualified as a surgeon in 1880, and was studying ophthalmology under Professor Hansen Grut from 1879-1885. From 1885 onwards he practised in Copenhagen. He was surgeon to the Royal Institute for the Blind for 35 years, and commander of the military clinics of ophthalmology in Copenhagen from 1894-1912. He held rank in the army medical department from 1891-1918, and his last six years of service were as Commander of the Garrison Hospital in Copenhagen, with the rank of Colonel. He also served the Board of Health for a great many years, and was its vice-president for 20 years. To our columns he contributed a paper on ophthalmia neonatorum in Denmark, and in 1938 we gave a short abstract of his experiences at the Royal Institute for the Blind.

Gordon Norrie was an authority on medical history, and particularly on the history of ophthalmology. His "Den Danske Oftalmologis Historie indtil aar 1900" appeared in 1925, and he was so kind as to send a copy to the writer of this note.

At the 450 years celebrations of the University of Copenhagen, he was created M.D. *honoris causa*.

The writer much enjoyed the friendly correspondence he had with Gordon Norrie. In it he always spoke with diffidence about his ability to write our language, but we never noticed much amiss. He was proficient in many languages, including French and German, and was a good Latin Scholar. We are happy to think that he was spared much suffering, bodily and mental, and that he maintained his youthful outlook to the end, in spite of his great age. His wife died in 1940. We are indebted to his son, Captain Gordon Norrie, for the facts recorded here.

The photograph we reproduce was taken in 1929.

R.R.J.

NOTES

Combating Trachoma in the Soviet Union

TRACHOMA has been known in Russia for centuries. Mention of it in literature can be found as far back as the XV century. The disease seems to have been imported by the Tartars during their invasion in the XIII century. The principal foci of trachoma were located in the region of the Middle Volga, in Transcaucasia and Central Asia.

The tsarist government took no steps to eradicate trachoma, no government measures having ever been undertaken in this direction. The only thing done was the organisation by a philanthropical society of temporary units for ophthalmological treatment. These bodies were sent to the foci of epidemics in order to estimate the incidence and the character of the disease, and to provide medical care.

The Soviet Revolution in 1917 brought with it a radical change in the social order of Russia, establishing entirely new conditions of life for the population. The control of trachoma was recognised as a matter of national concern. Due measures were taken to record the foci of infection and to elaborate a plan and adequate methods for the control of the disease. An institute for trachoma research was founded in Kazan. Examination of the population carried out on a large scale confirmed the widespread incidence of trachoma and the large number of cases which had lost their sight because of this disease. As an infection intimately connected with the conditions of life, trachoma was not only a source of misery to those who were stricken by it, but it also inflicted heavy losses upon the state as a whole, reducing the efficiency of, and even completely incapacitating large numbers of people in the prime of life. The Government issued a special decree concerning the measures of trachoma control, its general trend and character, and the scope of the work to be carried out. The decree authorised the Public Health Boards under definite conditions to impose compulsory treatment.

In the U.S.S.R. anti-trachoma measures are based on dispensary treatment; this method implies, in addition to sanitary, preventive and curative measures, a close approach of the practitioner to the population, to the very focus of infection, as well as obligatory co-operation of the population in the control of the disease. All measures are effected under a general plan, without any remission in the work lest the results already obtained should be lost.

The whole network of medical institutions of both in- and out-patient hospital type actively collaborate in anti-trachomatous measures in the U.S.S.R.; in the first place this refers to rural medical institutions and to physicians working in villages. In such localities as are the most severely infected by trachoma, new special trachoma-posts have been organised, situated within the focal area of the infection. These stations are staffed by specially trained nurses mostly chosen from among the local population, so that the language and customs of their patients are familiar to them. These nurses work under the supervision of physicians. The lead in all these activities is given by the ophthalmological and trachoma institutions in the various cities—Kazan, Ashkhabad, Alma-Ata, Leningrad, Kharkov, Odessa; the ophthalmological clinics of the medical institutes also participate directly both in scientific and curative work, helping the Public Health Boards in their organisational activities and in the control over the work carried on.

All the work is under the direction of the People's Commissariat of Health of the U.S.S.R. with the assistance of the Central Ophthalmological Institute of Moscow.

The network of ophthalmological establishments has reached a considerable development in this country. At the present time there are 12,000 beds for eye-cases, up to 4,500 trachoma-posts in villages, 15 trachoma dispensaries, 8 ophthalmological and trachoma-research institutes and 50 clinics for eye diseases. In addition to these special establishments which are continuously engaged in trachoma control, analogous work is carried on by rural physicians and medical assistants who in case of urgent need are helped by special anti-trachoma expeditions. During the present war such expeditions have been sent to the Turkmen, Tajik, Uzbek and Kazakh republics

The rural medical network and the ophthalmological establishments listed above continue their widescale work. Thus, 22,000.000 attendances by patients were recorded in 1943 at the trachoma-posts alone. But the latter do not confine their work to out-patient treatment: they engage in extensive and many-sided activity, involving inspection, and health education. Special attention is given to children starting from the earliest age, as well as to those drafted into army service. Trachoma patients are registered and given medical attendance at special establishments. In cases where young children are concerned, medical bodies are assisted by the child welfare institutes; if cases of trachoma are recorded among school children, the pediatric specialists and school physicians are invited to take part in the work. The children are regularly examined, as a preventive measure.

Regular widespread treatment of trachoma patients, which extends to more and more numerous cases has already given excellent results; very frequently the disease is arrested and many severe complications that might otherwise lead to blindness are prevented. There is a sharp drop in the incidence of blindness due to trachoma.

Along with the curative work, widescale preventive measures are in force in the U.S.S.R. The aim of this work is to get rid of those negative sides of life which are responsible for the spread of trachoma. In this part of the work the population must necessarily share; but the latter cannot be of real help unless they are familiar with the subject. They have to be taught a great deal about trachoma; how it is transmitted and what stimulates its spread, what must be done to avoid infection,

etc. This is why health education plays an important part among other measures of trachoma control. This kind of work is done by the medical personnel wherever they meet with a suitable audience, both in medical institutions and outside of them, at home or in industrial and agricultural enterprises. The work is carried on systematically and according to a general plan, by means of lectures and talks illustrated by films, by broadcasting, publication of posters, pamphlets, booklets, the organisation of exhibitions, etc.

As a result of this systematic work, the incidence of trachoma has declined steadily in the U.S.S.R. during recent years. This success is largely due to the rise in the cultural level and in the well-being of the population, including the peasants who have united into collective farms. A considerable reduction in the number of trachoma cases had been recorded throughout the U.S.S.R. as early as in 1914, just before the war broke out. Thus, for example, in the Chuvash Autonomous S.S.R., the incidence of trachoma fell within ten years by 75·4 per cent.; in the Autonomous Udmurt Republic by 66·3 per cent.; in the Mari Autonomous Republic by 78 per cent.; in the Mordovian Autonomous Republic by 74 per cent.; and in the Bashkirian Autonomous Republic by 71·7 per cent.

The present war, which involved the migration of considerable masses of population from the rear-front to the interior of the country might have been expected to produce a spread of trachoma, but nothing of the kind has been observed.

Experience has shown the dispensary method of trachoma control, as widely applied in the U.S.S.R., to be an adequate and highly efficient one. By its means it has proved possible within a rather short period of time to eradicate trachoma as a disease affecting vast numbers of the population.

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Honour

SIR ARNOLD LAWSON has been chosen President of the Royal Medical Benevolent Fund in succession to the late Sir Thomas Barlow.

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Princess Tsahai Memorial Hospital Fund

WE drew attention last year, p. 202, to an appeal for funds to erect this hospital in Ethiopia. The Hon. Secretary has recently visited the site and renews her appeal for this good cause. There is a crying need for a training school for nurses in connexion with the hospital. The buildings will also include provision for sick children and training for children's nurses. It is hoped to complete the hospital buildings in December of this year. The target aimed at is £100,000. Donations will be acknowledged by Lord Horder, the Hon. Treasurer of the fund, c/o Messrs. H. Reynolds and Co., Hon. Chartered Accountants, 1, Bloomsbury Court, W.C.1.

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Special Notice

WE are asked by the Ministry of Information to state that the fact that goods made of raw materials in short supply owing to war conditions are advertised in this journal should not be taken as an indication that they are necessarily available for export.